DESIGN AND DEVELOPMENT OF CAPLETS BEARING LAFUTIDINE AND DOMPERIDONE

Dissertation Submitted to

The Tamil Nadu Dr. M.G.R. Medical University, Chennai – 32.

In partial fulfillment for the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

Reg. No. 26103005

Under the guidance of

Dr. R. SAMBATH KUMAR, M.Pharm., Ph.D.

DEPARTMENT OF PHARMACEUTICS

J.K.K. NATTRAJA COLLEGE OF PHARMACY

Komarapalayam – 638 183

Tamil Nadu

MAY – 2012

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"DESIGN AND DEVELOPMENT OF CAPLETS BEARING LAFUTIDINE AND DOMPERIDONE",** submitted by the student bearing **Reg.No. 26103005** to "The Tamil Nadu Dr. M.G.R. Medical University", Chennai, in partial fulfillment for the award of degree of **MASTER OF PHARMACY** in **PHARMACEUTICS** was evaluated by us during the examination held on…….

Internal Examiner **External Examiner**

CERTIFICATE

This is to certify that the work embodied in this dissertation entitled **"DESIGN AND DEVELOPMENT OF CAPLETS BEARING LAFUTIDINE AND DOMPERIDONE",** submitted to "The Tamil Nadu Dr. M.G.R. Medical University", Chennai, in partial fulfillment for the award of degree of **MASTER OF PHARMACY** in **PHARMACEUTICS**, is a bonafide work carried out by **Mr. KADAM GOVING GANGADHAR, [Reg.No:26103005],** during the academic year 2011-2012, under the guidance and direct supervision of **Dr. R. SAMBATH KUMAR, M.Pharm., Ph.D.,** Professor & Head, Department of Pharmaceutics**,** J.K.K. Nattaraja College of Pharmacy, Komarpalayam.

Place: Komarapalayam
Date :

Dr. P. PERUMAL, M.Pharm., Ph.D., AIC
Professor and Principal,
J.K.K.Nattraja College of Pharmacy,
Komarapalayam – 638183, Tamil Nadu.

CERTIFICATE

This is to certify that the dissertation entitled, **"DESIGN AND DEVELOPMENT OF CAPLETS BEARING LAFUTIDINE AND DOMPERIDONE",** submitted to "The Tamil Nadu Dr. M.G.R. Medical University", Chennai, in partial fulfillment for the award of degree of **MASTER OF PHARMACY** in **PHARMACEUTICS**, is a bonafide work carried out by **Mr. KADAM GOVING GANGADHAR, [Reg.No:26103005],** during the academic year 2011-2012, under the guidance and direct supervision in the Department of Pharmaceutics, J.K.K. Nattaraja College of Pharmacy, Komarpalayam.

Place: Komarapalayam
Date:

Dr. Sambath Kumar, M.Pharm., Ph.D.,
Professor and Head
Department of Pharmaceutics,
J.K.K. Nattaraja College of Pharmacy,
Komarpalayam-638 183, Tamil Nadu.

.

.

DECLARATION

The work presented in this dissertation entitled **"DESIGN AND DEVELOPMENT OF CAPLETS BEARING LAFUTIDINE AND DOMPERIDONE",** was carried out by me under the direct supervision of **Dr. R. SAMBATH KUMAR, M.Pharm., Ph.D.,** Professor & Head, Department of Pharmaceutics**,** J.K.K.Nattraja College of Pharmacy, Komarapalayam, in the partial fulfillment for the award of the degree of Master of Pharmacy in Pharmaceutics.

This work is original and has not been submitted in part or full for the award of any other degree or diploma of any university.

Place: Komarapalayam

Date:

KADAM GOVING GANGADHAR

Reg. No: 26103005

Department of Pharmaceutics,

J.K.K.Nattraja College of Pharmacy,

Komarapalayam- 638183.Tamil Nadu

Dedicated to

My Beloved Parents

& dear brother

ACKNOWLEDGEMENT

At the outset, I am thankful to my **PARENTS** and God for blessing me with great strength and courage to complete my dissertation. Behind every success there are lots of efforts, but efforts are fruitful due to helping hands making the passage smoother. So, I am thankful to all those hands and people who made my work grand success.

I am proud to dedicate my humblest regards and deep sense of gratitude and heartfelt thanks to late **Thiru. J.K.K. NATARAJAH CHETTIAR, founder** of our college. I wish to express my sincere thanks to our most respectful correspondent **Tmt. N. SENDAMARAAI** and our beloved Managing Director **Mr. S. OMM SHARRAVANA,** B.Com, LLB. and Executive director **Mr. S. OM SINGARAVEL,** B.E., M.S. for enabling us to do the project work.

I express whole hearted gratitude to my guide **Dr. R. Sambath Kumar, M.Pharm., Ph.D.,** Professor and Head, Department of Pharmaceutics, J.K.K NATARAJA COLLEGE OF PHARMACY, KOMARAPALAYAM, for suggesting solutions to problems faced by me and providing indispensable guidance, tremendous encouragement at each and every step of this dissertation work. Without her advice and deep-rooted knowledge, this work would not have been a reality

I express my heartful thanks to our respectable and beloved **Dr. P. Perumal, M.Pharm., Ph.D., A.I.C., Principal, J.K.K. Nattraja College of Pharmacy, Komarapalayam.** For his indispensable support which enabled us to complete this task vast success.

My glorious acknowledgement to **Dr. K. SENGODAN, M.B.B.S.,** administrative officer for encouraging us in a kind and generous manner to complete this work.

I expresses my sincere thanks to **Mrs. S. Bhama,** M.Pharm., Ph.D., Assistant Professor, **Mr. K. Jaganathan,** M.Pharm., Lecturer, **Mr. R. Kanagasabai,** B.Pharm., M.Tech., Assistant. Professor, Department of Pharmaceutics, for their valuable help during my project.

My sincere thanks to **Mr. V. Rajesh**, M.Pharm, Ph.D., Assistant Professor and Head of the Department, **Mrs. M. Sudha,** M.Pharm., Lecture**, Dr. P. Ashok kumar, Ph.D,** Professor **and Mrs. R. Krishnaveni, M.Pharm,** Assistant professor**,** Department of Pharmacology for their valuable suggestions during my project.

My sincere thanks to **Mr. V. Sekar,** M.Pharm., Professor & Head., **Mr. S. Jayaseelan,** M.Pharm., Assistant Professor, **Mr. Boopathy,** M.Pharm., Assistant Professor, **Mr. Senthilraja,** M.Pharm. Assistant Professor, Department of Pharmaceutical Analysis for their valuable suggestions.

I express my sincere thanks to **Dr. P. Sivakumar,** M.Pharm., Ph.D.**,** Professor and Vice Principal, **Mr. M. Vijayabaskaran,** M.Pharm, Assistant Professor, **Mrs. P. Vaijayanthimala,** M.Pharm, Assistant Professor, Mrs**. K. Mahalakshmi**, M.Pharm. Lecturer, Department of Pharmaceutical Chemistry, for their valuable suggestion and inspiration.

My sincere thanks to **Dr. S. Sureshkumar,** M.Pharm., Ph.D., Professor & Head of the Department of Pharmacognosy and **Mr. M. K. Senthilkumar,** M.Pharm. Assistant Professor, Department of Pharmacognosy for their valuable suggestions.

I express my sincere thanks to **Mr. N. Venkateswara Murthy,** M.Pharm., Assistant Professor & Head, **Mr. Rajarajan,** M.Pharm., Lecturer. and **Ms. S. Thangamani**, M.Pharm., Lecturer, Department of Pharmacy practice for their valuable suggestion.

My sincere thanks to **Mr. N. Kadhiravel ,** M.C.A., for his help during the project. I am delighted to **Mrs. V. Gandhimathi,** M.A., M.L.I.S., Librarian.,

Mrs. S. Jayakla, B.A., Assistant., for providing necessary facilities from Library at the time of Work. I extend my thanks to **Mr. S. Venkatesan**, Storekeeper, **Mr**. **Manikandan**, computer lab Assistant, and I wish to thank **Mr. B. Muthu Kumaran, Mr. M.K. Ramesh** our lab assistants for their help during the project.

I am specially thankful to my senior SHYAM BHAI, AKASH BHAI, SANDEEP SIR, my classmates and Maharashtra friends.

I pay **tribute** to **my lovable parents, Mr. KADAM GANGADHAR RAMJI my father**, **Mrs. KADAM LAXMIBAI GANGADHAR my mother, and my sister Mrs. REVATI DANDEGAOANKAR** for lifting me up till this phase of life. I sincerely thank them for their love, trust, patience and support and bearing all kinds of stress to make me what I am.

It is very difficult task to acknowledge the services to thank all those gentle people. So I would like to thank all those people who have helped me directly or indirectly to complete this project work successfully.

Kadam Govind Gangadhar
Reg. No. 26103005

CONTENTS

LIST OF ABBREVIATIONS

S. No	Abbreviations	Description
1	#	Number
2	µm	Micrometer
3	**%**	Percentage
4	API	Active pharmaceutical ingredients
5	BCS	Biopharmaceutical Classification System
6	BP	British pharmacopoeia
7	CAS	Chemical Abstract Service
8	COA	Certificate of Analysis
9	FDA	Food And Drug Association
10	f_1	Dissimilarity factor
11	f_2	Similarity factor
12	G	Gram
13	g/ ml	Gram per milliliter
14	GARS	Generally Regarded as Safe
15	GC	Gas Chromatography
16	GI	Gastrointestinal Tract
17	HDPE	High density poly ethylene
18	HPLC	High performance liquid chromatography
19	HPMC	Hydroxy propyl methyl cellulose (Hypromellose)
20	ICH	International Conference on Harmonization
21	IP	Indian Pharmacopoeia
22	IPA	Isopropyl Alcohol

S. No	Abbreviations	Description
23	LOD	Loss on drying
24	MCC	Micro Crystalline Cellulose
25	mg	Milligram
26	mm	Millimeter
27	ml	Milliliter
28	N	Newton
29	NLT	Not Less Than
30	NMT	Not More Than
31	NSC	No significant change
32	OOS	Out of specification
33	PEO	Poly Ethylene Oxide
34	Ph Eur.	European Pharmacopoeia
35	ppm	Parts per million
36	PVP	Polyvinyl Pyrollidine
37	RH	Relative Humidity
38	rpm	Revolutions per minute
39	SR	Sustained release
40	USP	United States Pharmacopoeia
41	UV	Ultra Violet
42	w/w	Weight per weight
43	w/v	Weight per volume

INTRODUCTION

1.1 Overview of Gastro esophagal reflux disease (GERD):

Gastroesophageal reflux disease (GERD), gastro-oesophageal reflux disease (GORD), gastric reflux disease, or acid reflux disease is chronic symptoms or mucosal damage caused by stomach acid coming up from the stomach into the esophagus.

Gastro esophagal reflux disease (GERD) is a more serious form of gastro esophageal reflux (GER), which is common. Gastro esophageal reflux (GER) occurs when the lower esophageal sphincter (LES) opens spontaneously, for varying periods of time or does not close properly and stomach contents rise up into the esophagus. Gastro esophageal reflux (GER) is also called acid reflux or acid regurgitation, because digestive juices called acids rise up with the food. The esophagus is the tube that carries food from the mouth to the stomach. The lower esophageal sphincter (LES) is a ring of muscle at the bottom of the esophagus that acts like a valve between the esophagus and stomach.

Gastro esophagal reflux disease (GERD) is usually caused by changes in the barrier between the stomach and the esophagus, including abnormal relaxation of the lower esophageal sphincter, which normally holds the top of the stomach closed impaired expulsion of gastric reflux from the esophagus, or a hiatal hernia. These changes may be permanent or temporary ("transient"). [1]

When acid reflux occurs, food or fluid can be tasted in the back of the mouth. When refluxed stomach acid touches the lining of the esophagus it may cause a burning sensation in the chest or throat called heartburn or acid indigestion. Occasional GER is common and does not necessarily mean one has GERD. Persistent reflux that occurs more than twice a week is considered GERD and it can eventually lead to more serious health problems. People of all ages can have GERD. [2]

1. Causes, incidence, and risk factors: [2]

Reflux may cause symptoms, or it can even damage the esophagus.

The risk factors for reflux include:

1. Alcohol (Possibly)
2. Hiatal hernia (a condition in which part of the stomach moves above the diaphragm, which is the muscle that separates the chest and abdominal cavities).
3. Obesity: Some studies have shown that GERD is highly prevalent in patients who are morbidly obese and that a high body mass index (BMI) is a risk factor for the development of this condition[3]
4. Pregnancy
5. Scleroderma
6. Smoking

Heartburn and gastroesophageal reflux can be brought on or made worse by pregnancy and many different medications. Such drugs include:

1. Anticholinergics (e.g., for seasickness)
2. Beta-blockers for high blood pressure or heart disease
3. Bronchodilators for asthma
4. Calcium channel blockers for high blood pressure
5. Dopamine-active drugs for Parkinson's disease
6. Progestin for abnormal menstrual bleeding or birth control
7. Sedatives for insomnia or anxiety
8. Tricyclic antidepressants.

Symptoms:

More common symptoms are:

1. Feeling that food is stuck behind the breastbone
2. Heartburn or a burning pain in the chest (under the breastbone)
3. Nausea after eating

Less common symptoms are:

4. Bringing food back up (regurgitation)
5. Cough or wheezing
6. Difficulty swallowing
7. Hiccups
8. Hoarseness or change in voice
9. Sore throat

1.1.1 Pathophysiology of GERD: [3]

Schematically, the esophagus, lower esophageal sphincter (LES), and stomach can be envisioned as a simple plumbing circuit as described by Stein and coworkers. The esophagus functions as an antegrade pump, the LES as a valve, and the stomach as a reservoir. The abnormalities that contribute to GERD can stem from any component of the system.

1. Poor esophageal motility decreases clearance of acidic material.
2. A dysfunctional LES allows reflux of large amounts of gastric juice.
3. Delayed gastric emptying can increase volume and pressure in the reservoir until the valve mechanism is defeated, leading to GERD.
4. From a medical or surgical standpoint, it is extremely important to identify which of these components is defective so that effective therapy can be applied.

Esophagal defence mechanism:

Esophageal defense mechanisms can be broken down into 2 categories (i.e.,esophageal clearance and mucosal resistance). Proper esophageal clearance is an extremely important factor in preventing mucosal injury. Esophageal clearance must be able to neutralize the acid refluxed through the lower esophageal sphincter. (Mechanical clearance is achieved with esophageal peristalsis; chemical clearance is achieved with saliva). Normal clearance limits the amount of time the esophagus is exposed to refluxed acid or bile and gastric acid mixtures. Abnormal peristalsis can cause inefficient and delayed acid clearance.

Dysfunction of the lower esophagal spincter:

The lower esophageal sphincter (LES) is defined by manometry as a zone of elevated intraluminal pressure at the esophagogastric junction. For proper LES function, this junction must be located in the abdomen so that the diaphragmatic crura can assist the action of the LES, thus functioning as an extrinsic sphincter. In addition, the LES must have a normal length and pressure and a normal number of episodes of transient relaxation (relaxation in the absence of swallowing).

LES dysfunction occurs via one of several mechanisms: transient relaxation of the LES (most common mechanism), permanent LES relaxation, and transient increase of intra-abdominal pressure that overcomes the LES pressure.

Delayed gastric emptying:

The postulated mechanism by which delayed gastric emptying may cause GERD is an increase in gastric contents resulting in increased intragastric pressure and, ultimately, increased pressure against the lower esophageal sphincter. This pressure eventually defeats the LES and leads to reflux. However, objective studies have produced conflicting data regarding the role of delayed gastric emptying in the pathogenesis of GERD.

Hence the physiologic and anatomic factors that prevent the reflux of gastric juice from the stomach into the esophagus include the following**:**

1. The lower esophageal sphincter (LES) must have a normal length and pressure and a normal number of episodes of transient relaxation (relaxation in the absence of swallowing).

2. The gastro esophageal junction must be located in the abdomen so that the diaphragmatic crura can assist the action of the LES, thus functioning as an extrinsic sphincter. The presence of a hiatal hernia disrupts this synergistic action and can promote reflux.

3. Esophageal clearance must be able to neutralize the acid refluxed through the LES. (Mechanical clearance is achieved with esophageal peristalsis. Chemical clearance is achieved with saliva.)
4. The stomach must empty properly.

Esophagitis:[3]

Esophagitis (esophageal mucosal damage) is the most common complication of GERD, occurring in approximately 50% of patients.

A rapid urease test (RUT) is performed on the esophageal biopsy sample. The result is positive for esophagitis.

Esophagitis may be diagnosed using endoscopy, although it cannot always be appreciated on endoscopy. As many as 50% of symptomatic patients with GERD demonstrate no evidence of esophagitis on endoscopy. Still, documentation of this complication is important in diagnosing GERD. Degrees of esophagitis are described by the Savary-Miller classification as follows.

- Grade I – Erythema,
- Grade II – Linear nonconfluent erosions,
- Grade III – Circular confluent erosions,
- Grade IV – Stricture or Barrett esophagus.

Stricture: Strictures are advanced forms of esophagitis and are caused by circumferential fibrosis due to chronic deep injury. Strictures can result in dysphagia and a short esophagus. Gastroesophageal reflux strictures typically occur in the mid-to-distal esophagus and can be visualized on upper GI tract studies and endoscopy. Presence of a stricture with a history of reflux can also help diagnose GERD.

Barret esophagus: The most serious complication of long-standing or severe GERD is the development of Barrett esophagus. Barrett esophagus is present in 8-15% of patients with GERD and may progress to adenocarcinoma. Barrett esophagus is thought to be caused by the chronic reflux of gastric juice into the esophagus. It is defined by metaplastic conversion of the normal distal squamous esophageal epithelium to columnar epithelium.As with esophageal stricture; the presence of

Barrett esophagus indicates the need for surgical consultation and treatment (usually surgical fundoplication).

Treatment for GERD:[4,5,6]

The goals of treatment are:

- To bring the symptoms under control so that the individual feels better;
- Heal the esophagus of inflammation or injury;
- Manage or prevent complications such as Barrett's esophagus or stricture;
- And maintain the symptoms of GERD in remission so that daily life is unaffected or minimally affected by reflux.[4]

Lifestyle modification: [3, 4, 5,6,7,8]

It involves avoidance of factors that may bring on symptoms or make them worse, such as dietary changes or changes in daily routine. While diet does not cause GERD, reflux and its most frequent complaint of heartburn can be aggravated by foods. Certain medications can aggravate symptoms.

- **Position**: Gravity plays an important role in controlling reflux. The people who have a less than perfect lower esophageal sphincter (LES) find that if they lie down after a large meal, food comes back into the esophagus and heartburn occurs. Maintaining an upright posture until the meal is digested may prevent the heartburn. If heartburn occurs regularly at night, consider raising the head of the bed or inserting a triangular wedge to keep your esophagus above the stomach. Avoid exertion after a meal. It contracts the abdominal muscles and forces food through a weakened sphincter. This is especially true of tasks that require bending such as lifting or cleaning the floor.
- **Food**: A large meal will empty slowly from the stomach and exert pressure on the LES. It is best to eat early in the evening so that the meal is digested at bedtime. All meals should be eaten in relaxed stress-free surroundings. Smaller meals and an upright, relaxed posture should help minimize reflux.
- Certain foods compromise the sphincter's ability to prevent reflux, and are best avoided before lying down or exertion. These differ from person to person. Many person find that fats, onions, and chocolate as particularly troublesome. Alcohol

often provokes heartburn, by compromising the LES, irritating the esophagus, and by stimulating stomach acid production. Common beverages such as coffee (both caffeinated and decaffeinated), tea, cola, tomato juice, and citrus juice may aggravate symptoms by irritating the esophagus or stimulating stomach acid production**.** [7].

- Being overweight can promote reflux. Excess abdominal fat puts pressure on the stomach and the loss of even a moderate amount of weight makes many people feel better. Pregnancy is often troubled by heartburn, particularly in the first three months.

Prescription Medication:

Prescription medications to treat GERD and ulcers include drugs called H2 receptor antagonists (H2-blockers) and proton pump inhibitors which help to reduce the stomach acid which tends to exacerbate symptoms, and work to promote healing, as well as promotility agents which aid in the clearance of acid from the esophagus.

- **H_2 receptor antagonists**:

The H2 receptor antagonists are reversible competitive blockers of histamine at the H2 receptors, particularly those in the gastric parietal cells, where they inhibit acid secretion. They are highly selective, do not affect the H_1 receptors, and are not anticholinergic agents.[3]

Since the mid-1970's H_2-receptor antagonists have been used to treat GERD and ulcer disease. In GERD, H2-receptor antagonists improve the symptoms of heartburn and regurgitation and heal mild-to-moderate esophagitis. Symptoms are eliminated in somewhat over 50% of patients with twice a day prescription dosage of the H2-receptor antagonists. Healing of esophagitis may require higher dosing. These agents maintain remission in about 25% of patients. H2-receptor antagonists are generally less expensive than proton pump inhibitors and provide adequate, cost-effective approaches as the first-line treatment as well as maintenance agents in GERD and ulcer disease.[8]

The [H2]-receptor antagonists differ in their potency. This difference has no apparent clinical importance in peptic ulcer disease but may be a factor in their efficacy in GERD. Thus, higher doses of a less potent agent such as Cimetidine are

needed to demonstrate healing of erosive esophagitis. The more potent [H2]-antagonists, Ranitidine, Nizatidine and Famotidine, are more likely to be effective at standard duodenal ulcer doses. Ranitidine has been approved by the FDA at a dosage of 150 mg four times daily for healing erosive esophagitis and at 150 mg twice daily for relief of GERD symptoms. Nizatidine, the newest of the [H2]-receptor antagonists, was the first to be approved by the Food and Drug Administration for both symptom relief and healing of esophagitis at standard duodenal ulcer doses (150 mg twice per day). Recently Famotidine has also received approval for symptom relief and healing of erosive esophagitis at standard duodenal ulcer dosage (20 mg twice daily), and at a higher dosage (40 mg twice daily) for severe esophagitis.

A newly developed H_2 receptor antagonist Lafutidine is also used in the treatment of GERD and Peptic ulcer.[9] A recent crossover study in healthy volunteers did show that a single dose (10 mg) of this novel H2-RA is able to increase intragastric pH more quickly than a single dose (20 mg) of Rabeprazole, the fastest amongst the available PPIs.[10]

GER is a chronic illness often requiring long-term therapy. Because of their established safety records, the H2-receptor antagonists are the agents best suited for continuous long-term therapy. Reduction of H2-receptor antagonists to half doses at bedtime, in a fashion analogous to that used in maintenance therapy for duodenal ulcer is seldom successful for GERD. Most GERD patients require at least full split dose therapy when H2-antagonists are used for chronic continuous treatment. In summary, H2-blockers are effective in relieving heartburn and somewhat effective in heating esophagitis. Because of their excellent safety profile, they are still the primary prescription pharmacologic agents used in the treatment of GERD.

- **Proton pump inhibitors:**

Proton pump inhibitors (PPIs), such as omeprazole, and more recently lansoprazole, have been found to heal erosive esophagitis (serious forms of GERD) more rapidly than H_2 receptor antagonists. PPIs provide not only symptom relief, but also symptom resolution in most cases, even in those with esophageal ulcers. Studies have shown PPI therapy can provide complete endoscopic mucosal healing

of esophagitis at 6 to 8 weeks in 75% to 100% of cases. Daily PPI treatment provides the best long-term maintenance of esophagitis, particularly in keeping symptoms and disease in remission for those patients with moderate-to-severe esophagitis, plus this form of treatment has been shown to retain remission for up to five years. [8]

Although effective and safe, currently available PPIs are still far from the ideal antisecretory compound. Currently available PPIs have notable limitations.[11]

- **Prokinetic agents:**

Prokinetic agents, such as Metoclopramide (Reglan) , Bethanecol, and newer ones like Cisapride and Domperidone improve the motility of the esophagus and stomach and increase the lower esophageal sphincter (LES) pressure to help reduce reflux of gastric contents. They also accelerate gastric emptying.

Metoclopramide is a dopamine receptor antagonist that has been evaluated in the treatment of GERD in several trials. The few well-designed studies demonstrate an improvement in symptom control over placebo using metoclopramide 10 mg po q.i.d.[13] Metoclopramide is less effective, however, in both symptom control and healing of esophagitis when compared with H2RA therapy.[12]

Domperidone (Motilium^{R}) is a dopamine antagonist available from outside the United States or from sites within the U.S. via the Internet or Food and Drug Administration (FDA) referral. Unlike metoclopramide, domperidone does not cross the blood–brain barrier and thus has a better safety profile, with no significant CNS side effects and only a minor incidence of gynecomastia and galactorrhea. [12]

- **Antacids**: Antacids are a class of medications that act by directly neutralizing gastric acid. Calcium carbonate (Tums^{R}) is still a commonly used antacid, as is magnesium hydroxide (Mylanta^{R}, Maalox^{R}), and magnesium hydroxide with or without calcium (Rolaids^{R}). Powdered sodium bicarbonate is also available, but is less frequently used. Antacids provide rapid, but temporary, relief of heartburn (lasting 30 to 60 minutes) and thus may require frequent dosing.

- Alginic acid, a polysaccharide derived from seaweed, may be used in combination with antacids (Gaviscon^{R}) for the treatment of GERD. This agent

creates a viscous layer atop the gastric juice and may impede acid reflux by physically preventing acid from entering the esophagus while delivering coadministered antacids to the esophagus. Antacid/alginic acid combinations have been demonstrated to be superior to placebo for the relief of GERD symptoms and this therapy may also be used for the treatment of mild and infrequent heartburn.

Summary:

GERD is a common problem with a wide spectrum of clinical severity. A variety of tests are available to evaluate patients with GERD, and physicians must be aware of the type of information that each test can provide. Conservative measures employing nonpharmacologic therapy are appropriate for all patients. Initial pharmacologic therapy usually involves an H2-receptor antagonist or antacids. In many patients, long-term continuous therapy with an H2-receptor antagonist given in split doses is needed. Omeprazole is indicated for short-term therapy of severe erosive esophagitis and symptoms refractory to H2-receptor antagonists.

1.2 Oral drug delivery - A Overview

Since decades, illnesses are being treated clinically through delivery of drugs to the patients in the form of some pharmaceutical dosage forms like tablets, capsules, pills, creams, liquids, ointments, aerosols, injectable and suppositories. To achieve and maintain the concentration of an administered drug within therapeutically effective range, it is often necessary to take drug dosage several times in a day and these results in a fluctuating drug plasma levels. [15]

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience in administration, and cost-effective manufacturing process.[18]

The oral route of administration has wide acceptance and constitute 50-60 % of total drug formulations. This trend is still continuing since oral route is the most preferred route due to its several advantages including ease of ingestion, self-medication and most importantly, patient compliance.[2] In conventional oral drug delivery systems, there is little control over the release of drug from formulations. The effective concentration of drug at the target site can be achieved by intermittent administration of grossly excessive doses. This in most situations often results in constantly changing, unpredictable and often sub-therapeutic plasma concentrations leading to marked side-effects. [16]

Oral drug delivery is the most convenient route of administration among all the routes that have been explored for systemic delivery of drugs using different dosage forms. The oral absorption of drugs is often limited due to short gastric residence time (GRT) i.e., the time required for the content of the stomach to enter small intestine. This retention time is almost similar for particular species. In case of human beings it is 3 to 4 hours. Due to short transit time many of the conventional dosage forms are unable to deliver the active agents completely in the stomach. However, recent research findings showed that the use of gastro-retentive-dosage forms could avoid these associated problems.

Oral drug delivery is the most convenient route of administration among all the routes that have been explored for systemic delivery of drugs using different dosage forms. The oral absorption of drugs is often limited due to short gastric residence time (GRT) i.e., the time required for the content of the stomach to enter small intestine. This retention time is almost similar for particular species. In case of human beings it is 3 to 4 hours. Due to short transit time many of the conventional dosage forms are unable to deliver the active agents completely in the stomach. However, recent research findings showed that the use of gastro-retentive-dosage forms could avoid these associated problems. [18]

The development of pharmaceutical products for oral delivery, irrespective of its physical form, involves varying extent of optimization of dosage form characteristics within the inherent constraints of gastro intestinal (GI) physiology. Therefore the fundamental understanding of various disciplines,

including gastro intestinal (GI) physiology, pharmacokinetic, pharmacodynamic and formulation design are essential to achieve a systematic approach to the successful development of an oral pharmaceutical dosage form. The more sophisticated a delivery system, the greater are the complexities in design and optimization of the system. In any case, the scientific framework required for the successful development of an oral drug delivery system consists of a basic understanding of the following three aspects:

1. Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug
2. The anatomical and the physiological characteristics of the GIT
3. Physicochemical characteristics and drug delivery mode of the dosage form to be designed. [19]

PROBLEMS AND BARRIERS TO ORAL DRUG DELIVERY: [18]

The biggest problem in oral drug delivery is low and erratic bioavailability, which mainly results from one or more factors such as poor aqueous solubility, slow dissolution rate, low intestinal permeability, and instability in GI milieu, high first-pass metabolism through liver and/or intestine variable GI transit, and P-gp (Pico gram) mediated efflux. This, in turn, may lead to unreproducible clinical response or a therapeutic failure in some cases due to subtherapeutic plasma drug levels. Indeed, the incomplete and variable oral bioavailability will have its most serious impact for drugs with a narrow ‘‘therapeutic window’’ (e.g., theophylline, carbamazepine, quinidine, etc.) From an economic point of view, low oral bioavailability results in the wasting of a large portion of an oral dose, and adds to the cost of drug therapy, especially when the drug is an expensive one. It is, therefore, extremely important that these issues be considered and a suitable technique (or an animal model) be used while estimating the contributions from each factor responsible for low and/or variable bioavailability.[18]

Physicochemical Barriers:

1) **Aqueous solubility**:

It has long been recognized that before an orally administered drug becomes available for absorption at specific sites within the GI tract, it must be dissolved in the GI fluid. Since both the dissolution rate and the maximum amount of a drug that can be dissolved are dictated by the solubility of the drug in the medium aqueous solubility of a drug could be regarded as a key factor responsible for low oral bioavailability of poorly water-soluble drugs, thereby limiting their therapeutic potential.

2) **Lipophilicity:**

The lipid solubility or lipophilicity of drugs has long been recognized as a prerequisite for transcellular diffusion across the intestinal membrane. Traditionally, the lipophilicity of drug substances is expressed as the apparent partition coefficient or distribution coefficient (log P) between n-octanol and an aqueous buffer (pH 7.4), which is pH-dependent in the case of ionisable compounds. In general, compounds with low log P are poorly absorbed, whereas compounds with log P > 1 offer satisfactory absorption. It is important, however, that the drug possess an optimum lipophilicity, as too low or too high lipophilicity may result in less than optimum oral bioavailability.

3) **Aqueous boundary layer:**

The aqueous boundary layer or the unstirred water layer (UWL) is a more or less stagnant layer, about 30–100 mm in thickness, composed of water, mucus, and glycocalyx adjacent to the intestinal wall that is created by incomplete mixing of the lumenal contents near the intestinal mucosal surface.[33] The glycocalyx is made up of sulfated mucopolysaccharides, whereas mucus is composed of glycoproteins (mucin), enzymes, and electrolytes. Until recently, the resistance of the UWL to intestinal absorption was believed to be correlated to the effective intestinal permeability (Peff) values of the solutes; however, considerable evidence suggests instead that the available surface of the apical membrane of the intestinal mucosa is the main barrier for both actively and passively absorbedsolutes. It is also interesting to note that coadministration of food and prokinetic (motility inducing) agents such as cisapride tends to decrease the thickness of UWL by increasing segmental and

propagative contractions respectively, which may have implications for drug dissolution in the GI tract. The reverse is true for some viscous soluble dietary fibers, such as pectin, guar gum and sodium carboxymethylcellulose, which may increase the thickness of UWL by reducing intraluminal mixing and could possibly decrease the intestinalexsorption of lipophilic drugs like quinidine and thiopental.

Biological Barriers:

1) **Intestinal epithelial barrier**:

   The intestinal epithelial layer that lines the GI tract represents the major physical barrier to oral drug absorption.

2) **Gastrointestinal transit**:

   From the oral delivery standpoint, both gastric emptying time (GET) and small intestinal transit time (SITT) are considered important since the majority of drugs are preferentially absorbed in the upper parts of the GI tract (stomach, duodenum, and jejunum). Moreover, the stomach and intestines have a limited site for drug absorption. This is known as an ‘‘absorption window.’’ The relatively short GET (1–3 hours) and SITT (3–5 hours) thus provide limited time for drug absorption through the major absorption zone. These problems are further aggravated by the highly variable nature of the gastric emptying process, which can vary depending on several physiological factors, such as food, age, posture, exercise, body mass index, circadian rhythm, etc.; pathological factors, such as stress, diabetes, Crohn’s disease, and motility disorders; and pharmaceutical factors, such as size and density of formulation and coadministration of drugs like anticholinergic and prokinetic agents.

3) Food effect:

The coadministration of drugs with food is known to result in decreased, delayed, increased, or accelerated drug absorption, which may have pharmacokinetic and pharmacodynamic implications.

Metabolic and biochemical barriers:

1) **Presystemic Metabolism**:

Drugs administered orally are subject to presystemic metabolism via luminal metabolism, first pass intestinal metabolism, first pass hepatic metabolism.

P-Glycoprotein(p-Gp) and other efflux systems:

P-Gp can significantly contribute to the barrier function of the intestinal mucosa.

1.3 CURRENT TECHNOLOGIES IN ORAL DRUG DELIVERY: [18]

Over the last 3 decades, many novel oral drug therapeutic systems have been invented along with the appreciable development of drug delivery technology. Although these advanced Drug delivery system (DDS) are manufactured or fabricated in traditional pharmaceutical formulations, such as tablets, capsules, sachets, suspensions, emulsions, and solutions, they are superior to the conventional oral dosage forms in terms of their therapeutic efficacies, toxicities, and stabilities.

Based on the desired therapeutic objectives, oral DDS may be assorted into three categories: immediate-release preparations, controlled-release preparations, and targeted-release preparations. [18]

1. Immediate release preparations:[20]

The term “immediate release” pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation and/or the absorption of drug, is neither appreciably, nor intentionally, retarded by galenic manipulations.

DESIRED CRITERIA FOR IMMEDIATE RELEASE DRUG DELIVERY SYSTEM

Immediate release dosage form should-

In the case of solid dosage it should dissolve or disintegrate in the stomach within a short period.

1. In the case of liquid dosage form it should be compatible with taste masking.
2. Be portable without fragility concern.
3. Have a pleasing mouth feel.
4. It should not leave minimal or no residue in the mouth after oral administration.
5. Exhibit low sensivity to environmental condition as humidity and temperature.
6. Be manufactured using conventional processing and packaging equipment at low cost.

7. Rapid dissolution and absorption of drug, which may produce rapid onset of action.

POTENTIAL CANDIDATE FOR IMMEDIATE RELEASE ORAL DOSAGE FORM ARE:

Analgesics and anti inflammatory agent, Anthelmentics, Antibacterials, Antiarhythmic, Anti malarial, Anti protozoal , Anti ulcer, Anti thyroid agents, Anti migraine agents etc

Advantages of Immediate Release Drug Delivery System

An immediate release pharmaceutical preparation offers:

1. Improved compliance/added convenience.
2. Improved stability.
3. Suitable for controlled/sustained release actives.
4. Allows high drug loading.
5. Ability to provide advantages of liquid medication in the form of solid preparation.
6. Adaptable and amenable to existing processing and packaging machinery.
7. Cost- effective.

Excipients used in immediate release preparations: [14]

Excipients balance the properties of the actives in immediate release dosage forms. This demands a thorough understanding of the chemistry of these excipients to prevent interaction with the actives. These inactive food-grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product efficacy. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents.

Bulking material:

Bulking materials are significant in the formulation of fast-dissolving tablets. The material gastro intestinal contributes functions of a diluent, filler and cost reducer.

Lubricants:

Lubricants, though not essential excipients, can further assist in making these tablets more palatable after they disintegrate in the mouth. Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach level.

Flavours and sweetener:

Flavours and taste-masking agents make the products more palatable and pleasing for patients. The addition of these ingredients assists in overcoming bitterness and undesirable tastes of some active ingredients.

Super disintegrants:

A disintegrant is an excipient, which is added to a tablet or capsule blend to aid in the break up of the compacted mass when it is put into a fluid environment.

- **Advantages:**

1. Effective in lower concentrations
2. Less effect on compressibility and flowability
3. More effective intragranularly

- **Some super disintegrants are:**

1) Sodium Starch Glycolate (Explotab, primogel) used in concentration of 2-8 % & optimum is 4%. Mechanism of Action: Rapid and extensive swelling with minimal gelling.

2) Cross-linked Povidone (crospovidone) (Kollidone) used in concentration of 2-5% of weight of tablet. Completely insoluble in water.

Mechanism of Action: Water wicking, swelling and possibly some deformation recovery. Rapidly disperses and swells in water, but does not gel even after prolonged exposure. Greatest rate of swelling compared to other disintegrants.

3) Low-substituted hydroxyl propyl cellulose, which is insoluble in water. Rapidly swells in water. Grades LH-11 and LH-21 exhibit the greatest degree of swelling. Certain grades can also provide some binding properties while retaining disintegration Capacity. Recommended concentration 1-5% .

4) Cross linked carboxy methyl cellulose sodium (i.e. Ac-Di-sol) Croscarmellose sodium: Mechanism of Action: Wicking due to fibrous structure, swelling with minimal gelling. Effective Concentrations: 1-3% Direct Compression, 2-4% Wet Granulation.

Gas producing disintegrants:

Gas producing disintegrants are used especially where extra rapid disintegration or readily soluble formulation is required. Composition is based upon the same principles as those used for effervescent tablets, the most common being mixtures of citric & tartaric acids plus carbonates or bicarbonates.

In many instances lower concentration can be used with gas producing disintegrants than are required by other disintegrating agents. Certain peroxides that release oxygen has been tried, but they do not perform as well as those releasing carbon dioxide.

Conventional Technique Used In the Preparation of Immediate Release Tablets

* Tablet molding technique
* Direct compression technique
* Wet granulation technique
* Mass extrusion technique

- **Tablet Moulding:**

In this technology, water-soluble ingredients are used so that tablet disintegrate and dissolve rapidly. The powder blend is moistened with a hydro alcoholic solvent and is moulded in to tablet using compression pressure lower than used in conventional tablets compression. The solvent is then removed by air-drying. Moulded tablets have a porous structure that enhances dissolution.

- **Direct Compression Method:**

In this method, tablets are compressed directly from the mixture of the drug and excipients without any preliminary treatment. The mixture to be compressed must have adequate flow properties and cohere under pressure thus making pre-treatment as wet granulation unnecessary.

- **Wet Granulation Method:**

Wet granulation is a process of using a liquid binder to lightly agglomerate the powder mixture. The amount of liquid has to be properly controlled, as over-wetting will cause the granules to be too hard and under-wetting will cause them to be too soft and friable. Aqueous solutions have the advantage of being safer to deal with than solvent-based systems but may not be suitable for drugs which are degraded by hydrolysis.

- **Mass-Extrusion:**

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets.

Evaluation of immediate release tablets:

Evaluation of Blend:

The prepared blend is evaluated by following tests.

- Angle of repose
- Bulk density
- Tapped density
- Carr's index
- Hauser's ratio

Evaluation of Tablets:

The tablets are subjected to the following quality control tests:

- Weight variation
- Friability
- Hardness
- Disintegration

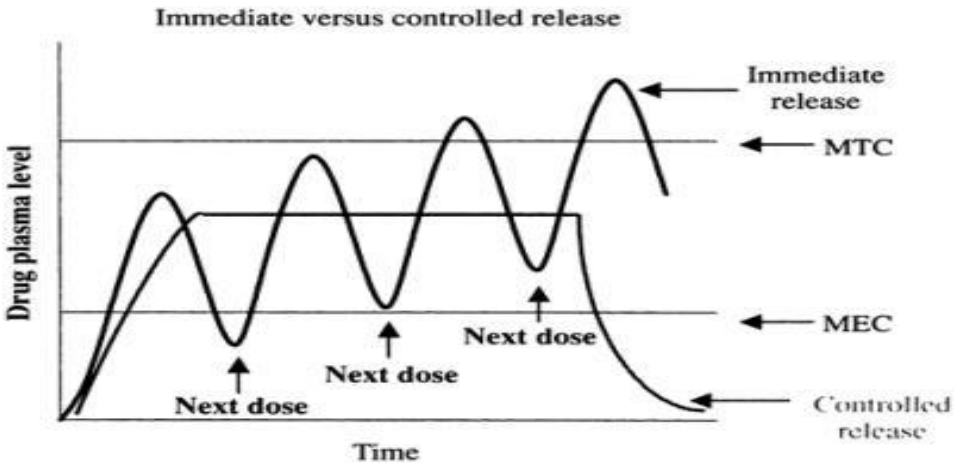
- In vitro Dissolution
- Stability studies

2. **Controlled release Preparations:**[41]

Over the past decades, the treatment of illness has been accomplished by administering drugs to the human body via various pharmaceutical dosage forms, like tablets. These traditional pharmaceutical products are still commonly seen today in the prescription and

over-the-counter drug market place. To achieve and maintain the drug concentration in the body within the therapeutic range required for a medication, it is often necessary to take this type of drug delivery system several times a day. This yields an undesirable ‘‘seesaw’’ drug level in the body.

Figure.No.1



A number of advancements have been made recently in the development of new techniques for drug delivery. These techniques are capable of regulating the rate of drug delivery, sustaining the duration of therapeutic action, and/or targeting the delivery of drug to a specific tissue. These advancements have already led to the development of several novel drug delivery systems that could provide one or more of the following benefits:

1. Controlled administration of a therapeutic dose at a desirable rate of delivery.
2. Maintenance of drug concentration within an optimal therapeutic range for prolonged duration of treatment.
3. Maximization of efficacy-dose relationship.

4. Reduction of adverse side effects.
5. Minimization of the needs for frequent dose intake.
6. Enhancement of patient compliance.

CLSIFICATION OF CONTROLLED RELEASE DRUG DELIVER SYSTEM:

Based on the technical sophistication of the controlled-release drug delivery systems (CrDDSs) that have been marketed so far, or that are under active development, the CrDDSs can be classified as follows:

1. Rate-pre-programmed drug delivery systems.
2. Activation-modulated drug delivery systems.
3. Feedback-regulated drug delivery systems.
4. Site-targeting drug delivery systems.

In this article, the scientific concepts and technical principles behind the development of this new generation of drug-delivery systems are outlined and discussed.

RATE-PREPROGRAMMED DRUG DELIVERY SYSTEMS:

In this group of CrDDSs, the release of drug molecules from the delivery systems has been pre-programmed at a specific rate profile. This is accomplished by system design, which controls the molecular diffusion of drug molecules in and/or across the barrier medium within or surrounding the delivery system. Fick's laws of diffusion are often followed. These CrDDSs can further be classified as follows:

1. Polymer membrane permeation-controlled drug delivery systems.
2. Polymer matrix diffusion-controlled drug delivery systems.
3. Polymer (membrane/matrix) hybrid-type drug delivery systems.
4. Micro reservoir partition-controlled drug delivery systems.

Polymer Membrane Permeation-Controlled Drug Delivery Systems:

In this type of CrDDS, a drug formulation is either totally or partially encapsulated in a drug reservoir compartment whose drug-releasing surface is covered by a rate-controlling polymeric membrane. The drug reservoir can be drug solid particles, a dispersion of drug solid particles, or a concentrated drug solution in a liquid- or solid-type dispersing medium

Polymer Matrix Diffusion-Controlled Drug Delivery Systems:[24]

The drug release from these system is time dependent and is given by,

$dQ/dt = (AC_rD_p/2t)^{½}$…….. (1.1)

Where,

dQ/dt is rate of drug release

A is loading dose

C_r is the drug solubility in polymer

t is time and

D_p is the drug diffusivity in Polymer.

Mode of release from hydrophilic matrix dosage form:

Hydrophilic matrix dosage forms essentially consist of a compressed blend of hydrophilic polymer and drug. According to the generally accepted mechanism, the drug release from hydrophilic matrix dosage forms starts when the tablet comes in contact with gastrointestinal fluid. The surface of the tablet hydrates to release exposed drug and at the same time form a viscous polymer mucilage or gel. This gel fills the interstices within the tablet, retarding further ingress of liquid.

The concentration of polymer within the hydrated layer ranges from dilution at the outer surface to around 90 % at the boundary of drug core. Within this layer, drug in various states of dissolution (un-dissolved in dilute solution; in saturated solution) is distributed amongst the other ingredients of the tablets.

Drug release occurs immediately from the surface (burst-effect) followed by diffusion and/or erosion of the hydrated layer. The relative proportions of drug released by diffusion and erosion are determined by the drug's solubility properties and by the physical and chemical nature of the hydrated polymer. This in turn is influenced by other factors, including drug characteristics, dissolution medium and others which have to be investigated.

Matrix type tablets:

Matrix tablets are one of the most widely used oral sustained-release systems containing a therapeutic agent, homogeneously dissolved or dispersed, in a compressed water-swellable, soluble or erodible core. The mechanism of drug release from polymeric matrices involves solvent penetration, hydration, swelling of the polymer, diffusion of the dissolved drug in the matrix and erosion of the gel layer. Initially the diffusion coefficient of the drug in the dehydrated hydrogel is very low, but increases significantly as the gel imbibes water. Interactions between water, polymer and drug are the primary factors for Sustained-release. Various formulation variables such as polymer grade, drug/polymer ratio, drug solubility and polymer particle size can influence drug release rate to a greater or lesser degree.

One of the most important stages in the formulation process is the selection of the polymeric matrix formers, due to the fact that the design of these systems have been focused on the concept of the polymeric hydration to protect the tablet from rapid disintegration and dissolution to delay the drug release rate.

One of the least complicated approaches to the manufacture of sustained-release dosage forms involves the direct compression of blends of drug, retardant material and additives to form a tablet in which drug is embedded. Alternately, retardant drug blends may be granulated prior to compression. The first class consists of retardants that form insoluble; the second class represents water-insoluble

materials that are potentially erodible; and the third class consists of polymers that form hydrophilic matrices. Loading doses are best included as the second layer of a two-layer tablet or in a coating applied to the matrix core.

Characteristics to be considered in the design of matrix system: [24]

1. The chemical nature of support (generally polymeric nets).
2. The physical state of the drug (dispersed in molecular or particulate form or both).
3. The matrix shape and alteration in volume as a function of time.
4. The route of administration (oral administration remains the most widely used but other routes are adaptable).
5. The release kinetics model.

Classification of Matrix Systems:

The classification of matrix systems can be based on several criteria namely- matrix structure, release kinetics (must be zero-order), controlled-release properties (diffusion, erosion and/or swelling) and chemical nature and properties of the applied materials. The various types of matrices are –

1. Mineral Matrix

- Drug retained in the support
- Drug adsorbed on the support

2. Hydrophilic Matrix

- Unlimited swelling, delivery by diffusion
- Limited swelling, controlled delivery through swelling

3. Inert Matrix

- Controlled delivery by diffusion

4. Lipidic Matrix

- Delivery by diffusion
- Delivery by surface erosion

5. Biodegradable Matrix

- Non-lipidic

Materials Used for Hydrophilic Matrix System

The polymers used for preparing hydrophilic matrix tablets are categorized into three groups -

1. Cellulose derivatives

Hydroxyethyl cellulose, hypromellose (HPMC) and sodium carboxymethyl cellulose.

2. Non-cellulosic natural or semisynthetic polymers

Agar-agar, guar gum, xanthan gum, alginates, polysaccharides of mannose and galactose, chitosan and modified starches.

3. Polymers of acrylic acid

Carbomers 934, 971P, 974P, 71G

HPMC Matrix Systems. [42, 43, 44, 45]

One of its most important characteristics is high swelling ability, which has a significant effect on the release kinetics of an incorporated drug. Diffusion, swelling, and erosion are the most important rate-controlling mechanism of commercially available controlled-release products.

The physiochemical properties of HPMC is strongly affected by –

i) The methoxy group

ii) The hydroxypropoxy group content and

iii) The molecular weight

Mechanism of drug release from HPMC matrices [46, 47]

1. At the beginning of the process, steep water concentration gradients are formed at the polymer-water interface resulting in water imbibition into the matrix.

2. Due to the imbibition of water, HPMC swells, resulting in dramatic changes of polymer and drug concentrations, and increasing dimensions of the system.
3. Upon contact with water the drug dissolves and diffuses out of the device.
4. With increasing water content the diffusion co-efficient of the drug increases substantially
5. In case of poor water-solubility, dissolved and non-dissolved drug coexist within the polymer matrix.
6. In case of high initial drug loadings, inner structure of the matrix changes significantly during drug release, becoming more porous and less restrictive for diffusion upon the depletion.

Advantages of hydrophilic matrix systems [49]

1. With proper control of manufacturing process, reproducible release profiles are possible.
2. There is an immediate-release of a small amount of active principle but there is no risk of dumping of large part of the dose.
3. Large capacity to incorporate drugs which allows them to release large doses.
4. The preparation processes are very simple. Matrix tablet can be made by direct compression or through conventional dry or wet granulation methods.
5. A class of inexpensive substances with official organizations acceptance.

Polymer (Membrane/Matrix) Hybrid-Type Drug Delivery Systems:

This type of CrDDS is developed with the objective of combining the constant drug release kinetics of polymer membrane permeation-controlled drug delivery systems with the mechanical superiority of polymer matrix diffusion-controlled drug delivery systems.

Microreservoir Partition-Controlled Drug Delivery Systems:

In this type of CrDDS, the drug reservoir is a suspension of drug solid particles in an aqueous solution of a water-miscible polymer, like polyethylene glycols. This forms a homogeneous dispersion of many discrete, unleachable,

microscopic drug reservoirs in a biocompatible polymer, like silicone elastomers. The microdispersion is achieved by applying a high-energy dispersion technique. Different shapes and sizes of drug-delivery devices can be fabricated from this microreservoir-type CrDDS by molding or extrusion techniques.

ACTIVATION-MODULATED DRUG DELIVERY SYSTEMS:

In this group of CrDDSs, the release of drug molecules from the delivery systems is activated by some physical, chemical, or biochemical processes and/or facilitated by energy supplied externally .The rate of drug release is then controlled by regulating the process applied or energy input. Based on the nature of the process applied or the type of energy used, these activation-modulated CrDDSs can be classified into the following categories:

1. Physical means:

a. Osmotic pressure-activated drug delivery systems.

b. Hydrodynamic pressure-activated drug delivery systems.

c. Vapor pressure-activated drug delivery systems.

d. Mechanical force-activated drug delivery systems.

e. Magnetics-activated drug delivery systems.

f. Sonophoresis-activated drug delivery systems.

g. Iontophoresis-activated drug delivery systems.

h. Hydration-activated drug delivery systems.

2. Chemical means:

a. pH-activated drug delivery systems.

b. pH-activated drug delivery systems.

c. Ion-activated drug delivery systems.

d. Hydrolysis-activated drug delivery systems.

3. Biochemical means:

a. Enzyme-activated drug delivery systems.

b. Biochemical-activated drug delivery systems.

FEEDBACK-REGULATED DRUG DELIVERY SYSTEMS:

In this group of CrDDSs, the release of drug molecules is activated by a triggering agent, such as a biochemical substance, in the body via some feedback mechanisms. The rate of drug release is regulated by the concentration of a triggering agent detected by a sensor built into the CrDDS.

SITE-TARGETING DRUG DELIVERY SYSTEMS:

Ideally, the path of drug transport should also be under control. Then, the ultimate goal of optimal treatment with maximal safety can be achieved. This can be reasonably accomplished by the development of a CrDDS with a site-targeting specificity.

CAPSULE – AS DOSAGE FORM:

Capsules are unit doses of drugs enclosed within soluble shells of gelatin or similar material, intended to swallow as a whole. Hard capsules were invented in 1833 in America. They were (and are today) made of gelatin and consist of two parts, a body and a cap (they were supplied ready made but were filled in the pharmacy). Capsules are available in many different sizes and shapes and can be used for administration of powders, semisolids and liquids. A capsule is a smooth, slippery, easy to swallow and tasteless shell of any convenient shape containing drugs. Capsules are made principally of gelatin blends and may contain small amounts of certified dyes, opacifing agents, plasticizers and preservatives.

Advantages of Capsule dosage form:

1. It is tasteless and particularly useful for drugs having unpleasant odour or taste.
2. It is economically produced in large quantities and has many pleasing colors.
3. It provides ready availability of the contained drug.
4. Manufacturing is easier as it uses minimal excipients and only little pressure is
5. Required while compacting as compared to tabletting.

Hard gelatin capsules consist of two parts: the base or body, the longer and lesser diameter portion and the cap, which is the shorter and slightly larger diameter portion. The cap is designed to slide over the base portion and form a snug seal. For human use, eight different sizes of gelatin capsules are generally used, ranging from the smallest.No.5 through the largest, No.000. The numerical designation for a capsule is arbitrary and bears no indication as to the capacity of the capsule. The capacity of a capsule is dependent upon the density and characteristics of the powders in the application. The capsule size only offers a relative volume designation.

Table.No.1. Empty hard gelatine capsule different size.

Size	Outer diameter (mm)	Height or locked length (mm)	Actual volume(ml)
000	9.97	26.14	1.37
00	8.53	23.30	0.95
0	7.65	21.7	0.68
1	6.91	19.4	0.50
2	6.35	18	0.37
3	5.82	15.9	0.30
4	5.31	14.3	0.21
5	4.91	11.1	0.13

Disadvantages:

Capsules are not suitable for drugs that are very soluble, such as salts (potassium chloride, potassium bromide, ammonium chloride).In these situations, the fluid penetrating the capsule rapidly dissolves the salt and creates a highly concentrated solution, which can cause nausea and vomiting when it contacts with the gastric mucosa. Strongly efflorescent or deliquescent materials are not suitable for capsules since efflorescent materials may cause capsules to soften, when water is lost. Strongly deliquescent powders may make the capsule shell brittle, when the moisture is extracted from the shell into the powder.

LITERATURE REVIEW

The oral drug delivery system has expanded over a past decade. With the development of new drug entities, the treatment of disease has become more organised with reduction in deaths due to various reasons like inappropriate dosage regimens, over dosing etc. The treatment nowadays has become more focussed with new dosage forms coming in and new combinations being given.

The present drug delivery system is developed for treatment of Gastro esophagal reflux disease and non ulcer dyspepsia.

The drug delivery system consists of administering the H_2 receptor antagonist i.e. Lafutidine and the prokinetic agent Domperidone together in such a way that the Lafutidine is given as immediate release form and Domperidone is provided in timed release form such that around 40% of the total dose of Domperidone is released as immediate release form and the remaining dose is released over a period of 24 hours. 0Many challenges were faced during the development of this drug delivery system. To overcome these challenges, prior art was reviewed and the final drug delivery system was designe.

Literature Review

1. ***Jain et al*** [50] US patent number US 2007/0160664 A1 describes a pharmaceutical composition comprising a Proton Pump inhibitor and Domperidone. In this invention Domperidone is provided in immediate release and a delayed release form. The solubility of delayed release form is increased in the intestine (pH 6.8) by incorporation an organic acid.

2. ***Badwan et al*** [51] US Patent number 5,646,131 describes methods for solubilising drugs using Cyclodextrins and Carboxylic acids. The invention describes improving the solubility of drugs which are insoluble in water preferably basic drugs by using organic carboxylic acids like Citric acid, Tartaric acid etc.

3. ***Broad et al*** [52] US patent number 5,705,190 describes methods for solubilising Basic drugs using organic carboxylic acids containing C_3-C_{20} carbon atoms. The preferred organic acids are Mallic acid, succinic acid, glutaric acid, glutamic acid and citric acid. Citric acid is the acid of choice in the present invention.

4. ***Khan et al*** [53] Prepared sustained release tablets of Domperidone using Hydroxy propyl methyl cellulose K100 LV. The drug release in this case was controlled by hydration of polymer used, which form gelatinous barrier layer at the surface of the matrix.

5. ***Nagarsenkar et al*** [53]describe coevaporates of Domperidone prepared using polymers by solvent evaporation technique. The drug release rate was dependent on concentration of polymer in the coevaporates. Dissolution of drug in phosphate buffer pH 6.8 increased as concentration of hydroxyl propyl methyl cellulose phthalate (HPMC-p) in coevaporates was increased.

6. ***Wan et al*** [55, 56] studied the action of hydroxypropylmethycellulose (HPMC) on aqueous penetration into matrices containing HPMC of varying viscosity and concentration. They reported that incorporation of HPMC into matrices improved wetting and enhanced water uptake into the matrices. As the molecular weight and concentration of HPMC increase the water uptake by system was greater. They concluded that the action of HPMC on aqueous uptake was depended on the molecular weight of HPMC.

7. ***Sung et al*** [57, 58] compared different viscosity grades of HPMC (Methocel® K100LV, K15, K100). The fastest release of drug was achieved for the K100LV formulation. The K4M formulation exhibited a slightly greater drug release than K15M and K100M. Due to the lack of a significant difference in the release profiles between K15M and K100M, the authors suggested a limiting HPMC viscosity of 15000cP, above which if viscosity increased, the release rate would no longer decrease. Similarly, formulations containing

higher HPMC viscosity grades had slower HPMC release, but no limiting HPMC viscosity was observed for polymer release.

8. Aronchick et al, [59] US patent number US 2010/0255096 A1 describes the composition and methods for transmucosal delivery of domperidone.

9. Kajino et al [60,61] described the use of pyrrole compounds including Lafutidine for the treatment of diseases like gastroesophagal reflux disease (GERD) , peptic ulcer, NSAIDs incduced gastric acid secretion etc.The invention also describes superiority of these compounds for the treatemnet of above mentioned diseases as compared to currently available propton pump inhibitors (PPIs).

10. Satyam et al US patent number US2011/0263526 A1 described the use of Nitric oxide releasing drugs including lafutidine for the treatment of GERD and other gastric disorders.

11. Hill et al [62]US patent number US 2010/0216754 described the use of H_2 receptor blockers including Lafutidine for the treatment of Gastroesophagal reflux disease (GERD) as well as for non Gastroesophagal reflux disease (NERD).

12. Plachetka et al, [63] US patent number US 2006/0165797 describes the use of alkaline buffering agents to deliver the drugs H_2 blocker Lafutidine to the acidic environment of stomach.It also describes the use of enteric coating composition to deliver the acid labile drugs to the intestine.

13. Hiroshi sato et al [65, 66] studied the effect of Lafutidine on gastric mucosa. Based on the study carried out by them it was concluded that Lafutidine is a novel, potent antisecretory agent having lost lasting antisecretory effect. Their findings say that:

Lafutidine is a novel histamine H2-receptor antagonist with both antigastric secretory and gastroprotective actions. In experimental animal models, it has been shown to have several unique characteristics; among them a potent

protective effect against indomethacin induced intestinal ulceration and necrotizing agent–induced gastroduodenal damage. The effect of the drug has been shown to be mediated at least partially by capsaicin-sensitive sensory neurons, independent of its antisecretory activity; the mucoprotective effect of Lafutidine was shown to be antagonized by hCGRP8-37 or attenuated by chemical deafferentation with a high dose of capsaicin. No data in the literature indicate that Lafutidine increases CGRP release from the afferent sensory neurons and increases the plasma concentration of CGRP.

14. Carmelo Scarpignato [64,67] (Laboratory of Clinical Pharmacology, Department of Anatomy, Pharmacology & Forensic Sciences, School of Medicine & Dentistry, and University of Parma, Italy) found that Lafutidine among other newly developed drugs is the most promising drug which can be used for the treatment of GERD and non ulcer dyspepsia.

They found that; conversely from Ranitidine and Famotidine, Lafutidine increases both daytime and night time intragastric pH in H. pylori-negative subjects and conversely from omeprazole (and other PPIs) its efficacy is not influenced by the CYP2C19 genotype status. Study in healthy volunteers did show that a single dose (10 mg) of Lafutidine is able to increase intragastric pH more quickly than a single dose (20 mg) of Rabeprazole, the fastest amongst the available PPIs. Both in fasting conditions and in the postprandial state, the duration of the antisecretory action was longer than that of the PPI because the drug maintained the pH over a given threshold for a sustained period of time.

AIM AND OBJECTIVE

The aim of the present study is to formulate a novel drug delivery based fixed dose combination therapy for the treatment of Gastroesophageal Reflux disease (GERD) and non ulcer dyspepsia (NUD).

The drug delivery system is a combination of a H_2 receptor blocker and a Prokinetic agent. Usually the H_2 blockers are administered once a day while prokinetic agents are prescribed thrice daily. The present formulation has been utilised to tackle the differences in dosing frequency of these two drugs. The formulation not only ensures patient convenience but also gives high relief rate.

The H_2 blocker given is Lafutidine, which is a newly developed drug, classified as 2^{nd} generation H_2 blocker. The prokinetic agent is Domperidone which relieves the dysmotility associated with GERD as well as NUD.

Lafutidine is provided in immediate release form which has antisecretory action, protects the gastric mucosa and thus helps in raising the intragastric pH. Both these actions of Lafutidine are longer as compared to PPI's as Lafutidine can maintain the intragastric pH over an extended period of time. [21]

Domperidone acts as a gastrointestinal emptying (delayed) adjunct and peristaltic stimulant. Domperidone facilitates gastric emptying and decreases small bowel transit time by increasing esophageal and gastric peristalsis and by lowering esophageal sphincter pressure.

Hence to summarize in brief, the various objectives that would be obtained from the current formulation are:

- To reduce the dosage frequency.
- To formulate a capsule this ensures patient convenience and also gives high relief rate.
- To provide cost–effective product.
- To formulate a combination therapy of a prokinetic agent and a gastric acid lowering compound which is more effective than mono therapy.

PLAN OF WORK

The present research work was planned as follows

1. **Literature survey**
2. **Procurement of Drug and suitable excipient**
3. **Selection of suitable excipients based on Literature search**
4. **Preformulation study**
   - **Active Pharmaceutical ingredient characterization:**

   i) Particle size analysis (Malvern Particle size measurement, sieve analysis.)

   ii) Flow properties (Bulk density, Tapped Density, Haunsner Ratio, Compressibility Index)

   iii) Solubility and standard curve

   - **Compatibility study**
   - **DSC Observation**
5. **Formulation**
   - Wet Granulation
6. **Evaluation**

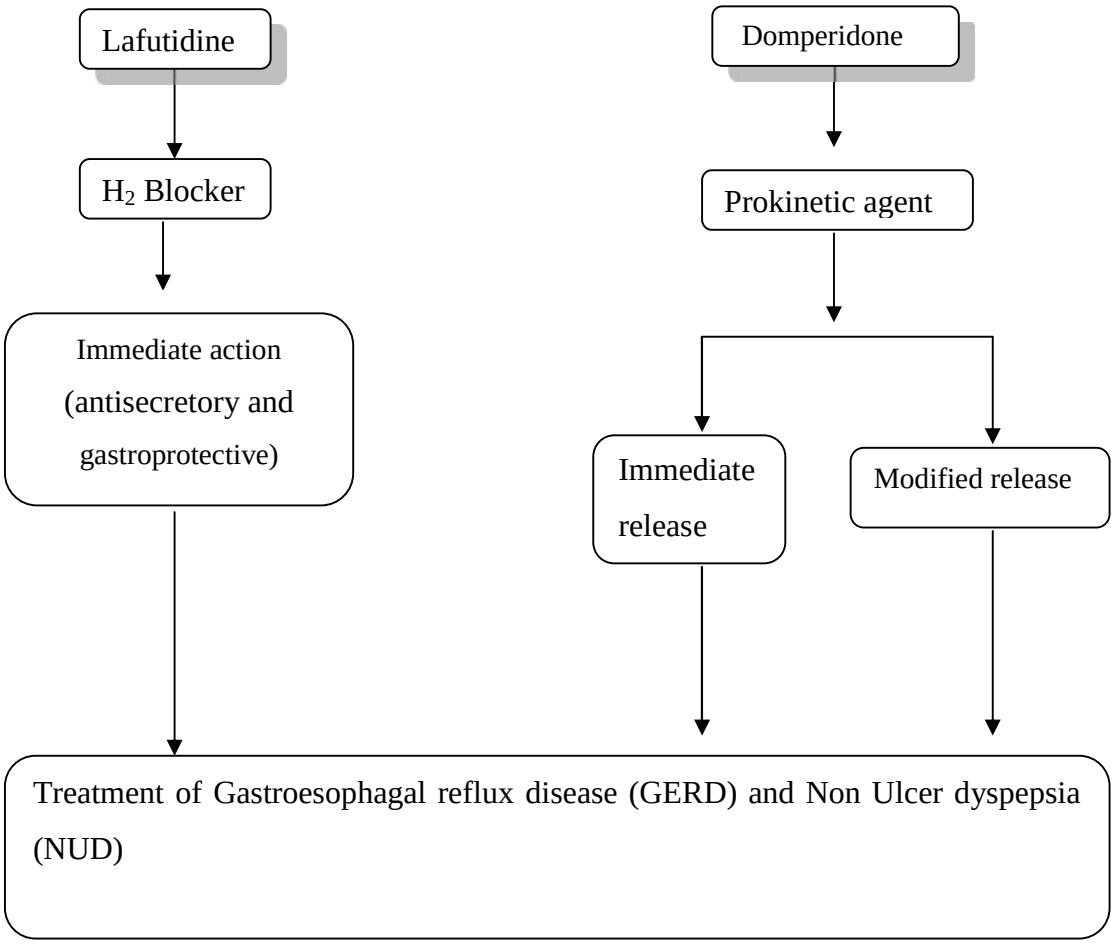
   a) Precompression Parameters
   - Moisture content
   - Flow properties
   - Sieve analysis

   b) Post compression Parameters
   - Weight Variation
   - Hardness
   - Thickness
   - Dissolution
   - Drug content

   c) Optimized formulation and reproducible batches.

   d) Short term accelerated Stability studies as per ICH guidelines.

Figure. No. 2 Flowchart plan of work



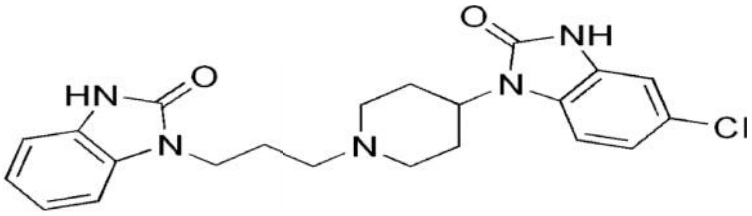
DRUG PROFILE

Domperidone: [30, 31, 32,33,34,35]

Proprietary name: Motilium®, Motillium , Motinorm and Costi.

Nonproprietary name: Domperidone.

IUPACname:5-chloro-1-(1-[3-(2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-1-yl)propyl]piperidin-4-yl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one



Molecular formula: $C_{22}H_{24}ClN_5O_2$.

Molecular weight: 425.9.

Appearance: A white or almost white powder.

Solubility: Practically insoluble in water, soluble in dimethyl formamide,Slightly soluble in alcohol and methanol. (Phr Eu)

Melting point: 242ºC to 248ºC**.**

Storage: Store protected from light.

BCS Class: Class II drug (Low solubility and high permeability).

Therapeutic category: Used to suppress nausea and vomiting or as a prokinetic agent.

CLINICAL PHARMACOLOGY OF DOMPERIDONE:

Phamacodynamics and mechanism of action (in detail?):

Domperidone is a specific blocker of dopamine receptors. It speeds gastrointestinal peristalsis, causes prolactin release, and is used as antiemetic and tool in the study of dopaminergic mechanisms.

Domperidone acts as a gastrointestinal emptying (delayed) adjunct and peristaltic stimulant. The gastroprokinetic properties of domperidone are related to its peripheral dopamine receptor blocking properties. Domperidone facilitates gastric emptying and decreases small bowel transit time by increasing esophageal and gastric peristalsis and by lowering esophageal sphincter pressure.

Antiemetic: The antiemetic properties of domperidone are related to its dopamine receptor blocking activity at both the chemoreceptor trigger zone and at the gastric level. It has strong affinities for the D2 and D3 dopamine receptors, which are found in the chemoreceptor trigger zone, located just outside the blood brain barrier, which among others regulates nausea and vomiting

Domperidone does not cross blood brain barrier as compared to other dopamine receptor antagonist. Hence it is free of extrapyramidal side effects.

Pharmacokinetics: [49]

Absorption

In fasting subjects, Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations at 30 to 60 minutes. The low absolute bioavailability of oral

domperidone (approximately 15%) is due to an extensive first-pass metabolism in the gut wall and liver. Although domperidone`s bioavailability is enhanced in normal subjects when taken after a meal, patients with gastro-intestinal complaints should take domperidone 15-30 minutes before a meal. Reduced gastric acidity impairs the absorption of domperidone. Oral bioavailability is decreased by prior concomitant administration of cimetidine and sodium bicarbonate. The time of peak absorption is slightly delayed and the area under curve (AUC) somewhat increased when the oral drug is taken after a meal.

Distribution

Oral domperidone does not appear to accumulate or induce its own metabolism; a peak plasma level after 90 minutes of 21 ng/ml after two weeks oral administration of 30 mg per day was almost the same as that of 18 ng/ml after the first dose .Domperidone is 91-93% bound to plasma proteins. Distribution studies

with radiolabelled drug in animals have shown wide tissue distribution, but low brain concentration.Small amounts of drug cross the placenta in rats.

Metabolism

Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. *In vitro* metabolism experiments with diagnostic inhibitors revealed that CYP3A4 is a major form of cytochrome P-450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation.

Excretion

Urinary and fecal excretions amount to 31 and 66% of the oral dose respectively. The Proportion of the drug excreted unchanged is small (10% of fecal excretion and approximately 1% of urinary excretion). The plasma half-life after a single oral dose is 7- 9 hours in healthy subjects but is prolonged in patients with severe renal insufficiency

V_d: 5.71 l/kg.

Plasma protein binding: 91-93%.

Presystemic metabolism: 85%.

Metablite: 5-Chloro-1, 3-dihydro-1-(4-piperidinyl)-2H-benzimidazol-2-one

Plasma half life: 7 hrs.

Dose: For oral dosage form (tablets).

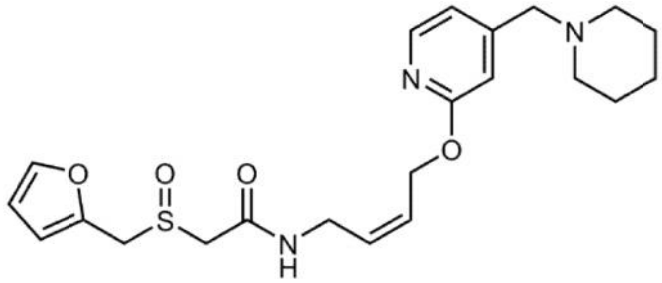
Treatment of gastrointestinal motility disorders:

Adults—10 milligrams (mg) three to four times daily. Some patients may require higher doses up to 20 mg three or four times daily.

Nausea and vomiting: Adults—20 milligrams (mg) three to four times daily

1.2 Lafutidine: [36, 37, 38, 39, 40]

IUPAC name : (±)-2-(furfurylsulfinyl)-N-[(Z)-4-[4-(piperidinomethyl)-2-pyridyl] oxy]-2-butenyl] acetamide



Molecular formula: $C_{22}H_{29}N_3O_4S$

Molecular weight: 431.56

Appearance: Lafutidine is a yellowish white crystalline powder with slight peculiar odour.

Solubility: It is freely soluble in acetic acid, slightly soluble in methanol, slightly soluble in ethanol (99.5), very slightly soluble in diethyl ether and practically insoluble in water.

Melting Point: 96-99ºC

Moisture absorbability:

Storage: store protect from light.

BCS class: Class II drug (Low solubility, High permeability)

Therapeutic category: It is a novel Histamine H_2 receptor antagonist with a potent and long lasting anti acid secretary effect and also gastro protective effect.

CLINICAL PHARMACOLOGY OF LAFUTIDINE:

Pharmacodynamics and mechanism of action:

Lafutidine is protective against experimental gastric lesions even in the presence of supplementary potent antisecretory therapy, suggesting that it has a direct gastroprotective effect in addition to its antisecretory properties. Lafutidine reduces esophageal injury in the gastric acid reflux model, apart from its antisecretory effect. This protective effect is abolished by selectively ablating CSAN, antagonism of CGRP and inhibition of NO synthase, suggesting that the capsaicin pathway is integral to Lafutidine's protective properties.

Pharmacokinetic Parameters:

Protein binding: 15-20%.

Half life: 2-3hr.

Absorption constant (K_a): 0.956 hr^{-1}

Elimination constant (K_{el}): 0.329 hr^{-1}

Volume of distribution (V_d): 42.46 lit.

Clearance (Cl): 12.97 l/hr.

C_{max} :133.9 (ng/ml).

T_{max} : 1.844 hr (article).

Dose:

Gastric and duodenal ulcers.

Adult*:* 10 mg bid, once after breakfast, once after evening meal or before sleeping. Adjust dose according to patient's age and symptoms.

Stomal ulcers

Adult*:* 10 mg bid, once after breakfast, once after evening meal or before sleeping. Adjust dose according to patient's age and symptoms.

Gastric mucosal lesions

Adult*:* 10 mg once daily, after evening meal or before sleeping. Adjust dose according to patient's age and symptoms.

Pre-anaesthetic medication Adult*:* 10 mg before sleeping on the day before operation, and 10 mg 2 hr before introduction of anaesthetic on the day of operation.

1. Excipient Profile:[14]

2.1. Cellulose, Microcrystalline:

Non-proprietary Names:

BP: Microcrystalline cellulose**,**

PhEur: Cellulosum microcritsallium,

USPNF: Microcrystalline cellulose

Synonyms: Avicel PH; Celex; cellulosic gel; Celphere; Ceolus sKG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulosel; Vivapur.

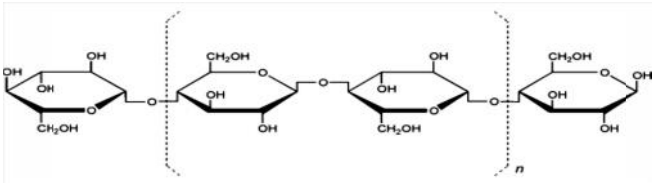
Chemical name: Cellulose.

CAS Registry Number: 9004-34-6.

Empirical Formula: [$C_6H_{10}O_5$**]** n.

Molecular Weight: ~36000 Where n=220.

Structural Formula:



Functional Category: Absorbent, suspending agent, tablet and capsule diluent; tablet disintegrate.

Application in Pharmaceutical Formulation or Technology:

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compressing process. In addition to its use as binder/diluents, in tableting. Microcrystalline cellulose is also used in cosmetics and food products.

Solubility: Slightly soluble in 5% W/V Sodium Hydroxide solution; practically insoluble in water, dilute acids and most organic solvents.

Incompatibilities: Microcrystalline cellulose is incompatible with strong oxidizing agents. Microcrystalline cellulose also has some lubricant and disintegrates properties that make it useful.

2.2 Hypromellose

Nonproprietary Names:

BP: Hypromellose,

JP: Hydroxypropyl methylcellulose,

PhEur: Hypromellosum,

USP: Hypromellose.

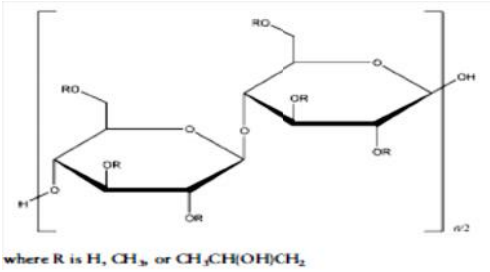
Synonyms: cellulose, hydroxypropyl methyl ether; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose.

Chemical Name: Cellulose, 2-hydroxypropyl methyl ether.

CAS Registry Number: [9004-65-3].

Molecular Weight: 10 000–1 500 000.

Structural Formula:



where R is H, CH_3, or $CH_3CH(OH)CH_2$

Functional Category: Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

Applications in pharmaceutical formulations:

Hypromellose is widely used in oral and topical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as an extended-release tablet matrix. Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions. Lower-viscosity grades are used in aqueous film- coating solutions, while higher-viscosity grades are used in organic solvents.

Hypromellose is also used as a suspending and thickening agent, emulsifier, suspending agent, and stabilizing agent in topical gels and ointments.

Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. It is also widely used in cosmetics and food products.

Solubility: Soluble in cold water; practically insoluble in chloroform, ethanol (95%) and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.

Incompatibilities: Hypromellose is incompatible with some oxidizing agents.

2.3 Magnesium Stearate

Nonproprietary Names:

BP: Magnesium stearate,

JP: Magnesium Stearate,

PhEur: Magnesii stearas,

USPNF: Magnesium stearate.

Synonyms: Magnesium octdecanoate; octadeconoic acid, magnesium salt; striate acid, magnesium salt.

Chemical name: Octadeconoic acid magnesium salt.

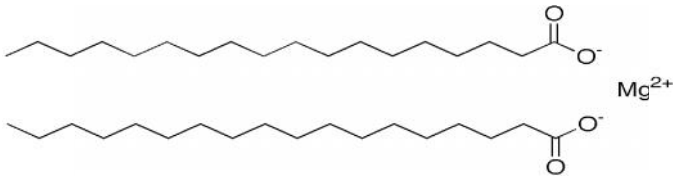
CAS Registry Number: [557-04-0].

Empirical Formula: $C_{36}H_{70}MgO_4$.

Molecular Weight: 591.34.

Structural Formula: $[CH_3 (CH_2)_{16}COO]_2 Mg$.

Structural Formula:



Functional Category: Tablet and capsule lubricant.

Application in Pharmaceutical Formulation or Technology:

agnesium striate is widely used in cosmetics, food and pharmaceutical formulation. It is primarily used as a lubricant in capsule and tablet manufacture at concentration between 0.25% and 5% w/w. It is also used in barrier creams.

Solubility: Practically insoluble in ethanol, ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Incompatibilities: Incompatible with strong acids, alkalies, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

2.4 Croscarmellose sodium:

Non proprietary names:

BP: Croscarmellose Sodium

JP: Croscarmellose Sodium

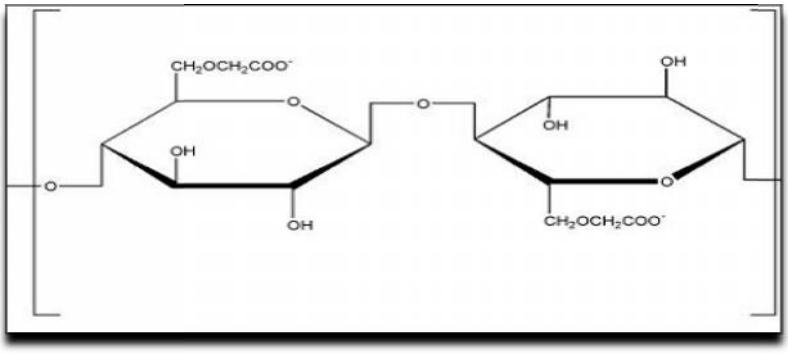
PhEur: Croscarmellose Sodium

USP-NF: Croscarmellose Sodium

Synonyms:

Ac-Di-Sol, Cross-linked Carboxy methyl cellulose (CMC) Sodium, Explocel, Modified Cellulose Gum, Nymcel ZSX, Primellose, Vivosol.

Structural formula;



Applications in Pharmaceutical Formulation or Technology:

As a disintegrant for tablets (wet granulation and direct compression), capsules and granules at a concentration of 2-5%.

Table.No.2 :Uses of Croscarmellose Sodium.

Use	Concentration (%)
Emulsifying agent	0.25 – 1.0
Gel – forming agent	3.0 – 6.0
Injections	0.05 – 0.75
Oral Solutions	0.1 – 1.0
Tablet Binder	1.0 – 6.0

2.5 Colloidal silicon dioxide (Arosil):

Non Proprietary Names:

BP: Colloidal Anhydrous Silica

JP: Light Anhydrous Silicic Acid

PhEur: Silica, Colloidal Anhydrous

USP-NF: Colloidal Silicon Dioxide

Synonyms:

Aerosil, Cab-O-Sil, Cab-O-Sil M-5P, colloidal silica, fumed silica, light anhydrous silicic acid, silicic anhydride, silicon dioxide fumed, Wacker HDK.

Chemical Name and CAS Registry Number: Silica [7631-86-9].

Empirical Formula and Molecular Weight: SiO_2, 60.08

Functional Category:

Adsorbent, anticaking agent, emulsion stabilizer, glidant, suspending agent, tablet disintegrant, thermal stabilizer, viscosity-increasing agent**.**

Applications in Pharmaceutical Formulation or Technology:

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products, Colloidal silicon dioxide is also used as a tablet disintegrant and as an adsorbent dispersing agent for liquids in powders. Colloidal silicon dioxide is frequently added to suppository formulations containing lipophilic excipients to increase viscosity, prevent sedimentation during molding and decrease the release rate.

Table.No.3: Uses of colloidal silicon dioxide.

Use	**Concentration (%)**
Aerosols	0.5 – 2.0
Emulsion stabilizer	1.0 – 5.0
Glidant	0.1 – 0.5
Suspending and thickening agent	2.0 – 10.0

2.6 Isopropyl Alcohol

Nonproprietary Names:

BP: Isopropyl alcoh,

JP: Isopropanol,

PhEur: Alcohol isopropylicus,

USP: Isopropyl alcohol

Synonyms: Dimethyl carbinol; IPA; isopropanol; petrohol; 2-propanol; sec-propyl alcohol.

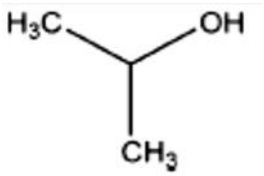
Chemical Name: Propan-2-ol.

CAS Registry Number: [67-63-0].

Empirical Formula: C_3H_8O.

Molecular Weight: 60.1.

Structural Formula



Functional Category: Disinfectant; solvent.

Applications in Pharmaceutical Formulation or technology:

Isopropyl alcohol is used in cosmetics and pharmaceuticals as a solvent. Isopropyl alcohol is used as a solvent for tablet film-coating and tablet granulation. Isopropyl alcohol used as a topical disinfectant.

Solubility: Miscible with benzene, chloroform, ethanol, ether, glycerin, and water. Soluble in acetone; insoluble in salt solutions.

Incompatibilities: Incompatible with oxidizing agents such as hydrogen peroxide and nitric acid, which cause decomposition. Isopropyl alcohol may be salted out from aqueous mixtures by the addition of sodium chloride, sodium sulfate, and other salts, or by the addition of sodium hydroxide.

2.7 Lactose monohydrate:

1. **Synonyms:**

4-O-beta-D-Galactopyranosyl-D-glucose, (alpha)-Lactose, Milk Sugar,

Milk Sugar, Lactose Monohydrate.

2. **Chemical Name:**

Lactose, Monohydrate.

3. **Chemical Formula:**

$C_{12}H_{22}O_{11}$. H_2O

5. **Molecular Weight:** 360.3

Table.No.4: Typical Properties of Lactose Monohydrate

Properties	Range
pH	5.0 -7.5
Angle of repose	40 ^{o}
Bulk density	0.22 g/cm^3
Tapped density	0.45 g/cm^3
True density	0.435-0.562 g/cm^3
Melting point	214C (417F)
Specific gravity	1.53

6. Applications in Pharmaceutical Formulation or Technology:

Lactose Monohydrate is widely used in pharmaceuticals, primarily as a diluent in oral tablet and capsule formulations where it is used in both wet-

granulation and direct compression processes. In addition to it has some lubricant and disintegrant properties that make it useful in tabletting.

Table.No.5: Uses of Lactose monohydrate

Use	Concentration (% w/w)
Adsorbent	20-90
Antiadherants	5-15
Capsule binder/diluents	20-90
Tablet disintegrants	5-15
Tablet binder/diluents	20-90

7. Solubility:

Soluble in water.

8. Description:

Lactose Monohydrate is a purified, white to off-White, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

2.7 Starch

1. **Nonproprietary Names:**

   BP: Maize starch, Potato starch, Rice starch, Wheat starch, JP: Corn starch, PhEur: Maydis amylum (maize starch), USPNF: Corn starch Tapioca

2. **Synonyms:**

   Amido, amidon, amilo, amylum, *Aytex P*, C*PharmGel, *Fluftex W*, Instant Pure-Cote, *Melojel*, Meritena, *Paygel 55*.

3. **Chemical Name and CAS Registry Number:**

   Starch, [9005-25-8].

4. Empirical Formula and Molecular Weight:

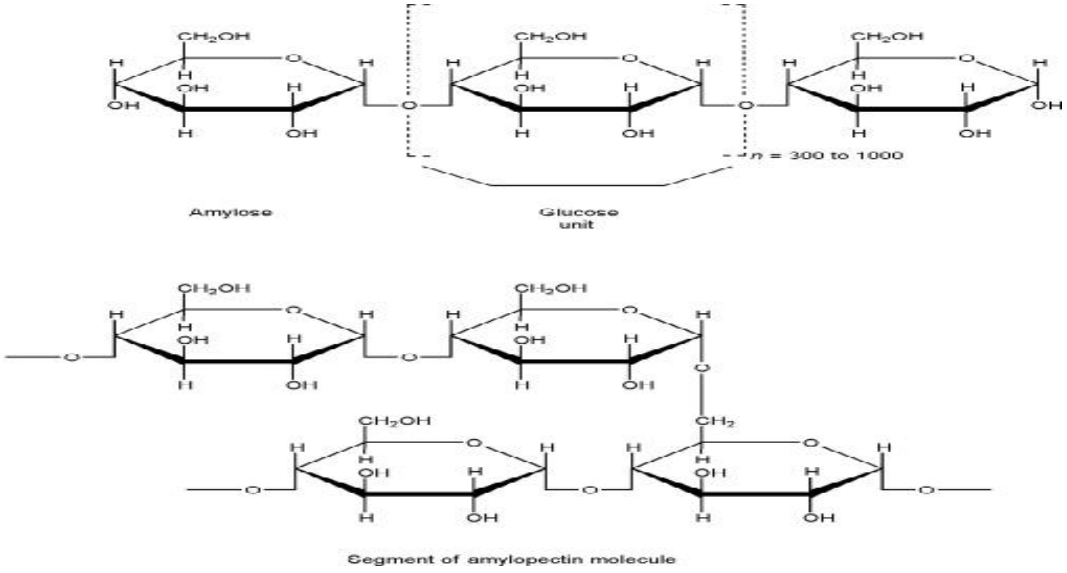
$(C_6H_{10}O_5)_n$ 50, 000–1,60, 000.

Where n = 300–1000.

5. Functional Category:

Glidant; tablet and capsule diluents; tablet and capsule disintegrants; tablet binder.

6. Structural Formula:



7. Applications in Pharmaceutical Formulation or Technology:

Starch is used as an excipient, primarily in oral solid-dosage formulations where it is utilized as a binder, diluent, and disintegrant.

As a diluent, starch is used for the preparation of standardized triturates of colorants or potent drugs to facilitate subsequent mixing or blending processes in manufacturing operations. Starch is also used in dry-filled capsule formulations for volume adjustment of the fill matrix.

In tablet formulations, freshly prepared starch paste is used at a concentration of 5–25% w/w in tablet granulations as a binder. Selection of the quantity required in a given system is determined by optimization studies, using parameters such as granule friability, tablet friability, hardness, disintegration rate, and drug dissolution rate.

Starch is one of the most commonly used tablet disintegrants at concentrations of 3–15% w/w. However, unmodified starch does not compress well and tends to increase tablet friability and capping if used in high concentrations. In granulated formulations, about half the total starch content is included in the granulation mixture and the balance as part of the final blend with the dried granulation. Also, when used as a disintegrant, starch exhibits type II isotherms and have a high specific surface for water sorption.

8. Description:

Starch occurs as an odorless and tasteless, fine, white-colored powder comprising very small spherical or ovoid granules whose size and shape are characteristic for each botanical variety

9. Solubility:

Practically insoluble in cold ethanol (95%) and in cold water. Starch swells instantaneously in water by about 5–10% at 37°C. Polyvalent cations produce more swelling than monovalent ions, but pH has little effect.

2.8 Citric acid monohydrate

1. Nonproprietary Name:

BP: Citric Acid Monohydrate

JP: Citric Acid Hydrate

PhEur: Citric Acid Monohydrate

USP: Citric Acid Monohydrate.

2. Synonyms:

Acidum citricum monohydricum; E330; 2-hydroxypropane-1,2,3-tricarboxylic acid monohydrate.

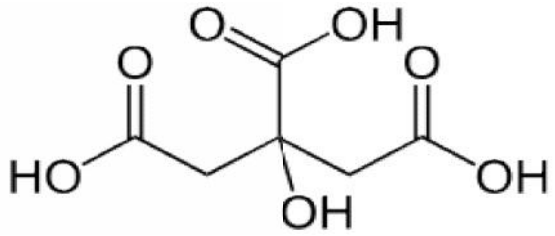
3. Chemical Name :

2-Hydroxy-1, 2, 3-propanetricarboxylic acid monohydrate.

4. Empirical Formula and Molecular Weight:

$C_6H8O_7H_2O$, 210.14

5 Structural Formula:



6. Functional Category:

Acidifying agent; antioxidant; buffering agent; chelating agent; flavor enhancer; preservative.

7. Applications in Pharmaceutical Formulation or Technology:

Citric acid (as either the monohydrate or anhydrous material) is widely used in pharmaceutical formulations and food products, primarily to adjust the pH of solutions. It has also been used experimentally to adjust the pH of tablet matrices in enteric-coated formulations for colon-specific drug delivery. Citric acid monohydrate is used in the preparation of effervescent granules, while anhydrous citric acid is widely used in the preparation of effervescent tablets.Citric acid has also been shown to improve the stability of spray-dried insulin powder in inhalation formulations.

In food products, citric acid is used as a flavor enhancer for its tart, acidic taste. Citric acid monohydrate is used as a sequestering agent and antioxidant synergist; see Table I. It is also a component of anticoagulant citrate solutions. Therapeutically, preparations containing citric acid have been used to dissolve renal calculi.

2.8 Povidone:

1. **Nonproprietary Names:**

BP: Povidone

JP: Povidone

PhEur: Povidone

USP: Povidone

2. **Synonyms:**

E1201; Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; povidonum; Povipharm; PVP; 1- vinyl-2-pyrrolidinone polymer.

3. **Chemical Name:**

1-Ethenyl-2-pyrrolidinone homopolymer

4**. Empirical Formula and Molecular Weight:**

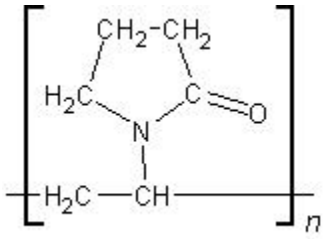
$(C_6H_9NO)_n$; 2500–3 000 000

The USP 32 describes povidone as a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the differing degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a K-value, in the range 10–120.

Table.No.6: Approximate molecular weights for different grades of Povidone

K-value	Approximate molecular weights
12	2500
15	8000
17	10000
25	30000
30	50000
60	400000
90	1000000
120	300000

5. Structural formula:



6. Functional Category:

Disintegrant; dissolution enhancer; suspending agent; tablet binder.

7. Applications in Pharmaceutical Formulation or Technology:

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes. Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations, and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms.(4–6) Povidone solutions may also be used as coating agents or as binders when coating active pharmaceutical ingredients on a support such as sugar beads. Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble drugs may increase by mixing with povidone.

8 Uses:

Table.No.7: Uses of Povidone

Use	Concentration (%)
Carrier for Drug	10-25
Dispersing agent	Up to 5
Eye drops	2-10
Suspending agent	Up to 5

EXPERIMENTAL WORK

1. Characterisation of Active pharmaceutical Ingredient (API):

a) Organoleptic evaluation:

This includes recording of colour, odour, and taste of the drug using descriptive terminology. Record of colour of early batches is very useful in establishing appropriate specifications for later production. Drugs generally have a characteristic odours and tastes. Unpleasant ones are masked later during formulation.

Table.No.8: APIs Organoleptic evaluation results

Tests	Lafutidine	Domperidone
Colour	Yellowish white	White
Odour	Peculiar odour	No odour

1. Bulk drug Characterisation:

a) Flow properties:

Angle of repose: [23]

Angle of repose has been used in several branches of science to characterize flow properties of solids. Angle of repose is a characteristic related to interparticulate friction or resistance to flow between particles. This is the maximum angle possible between surface of pile of powder or granules and the horizontal plane.

$\tan \theta = h / r$ …….(1)

$\theta = \tan^{-1} h / r$ …….. (2)

Where, θ = angle of repose, h = height of heap, r = radius of base of heap circle.

A funnel was fixed at a height approximately 2-4 cm over the platform. The loose powder was slowly passed along the wall of funnel, till the tip of powder cone so formed just touched the tip of funnel stem. Angle of repose was then determined by measuring the height of the cone of powder and radius of the circular base of powder heap.

Table.No.9: Flow properties and corresponding angles of repose.

Flow property	Angles of repose
Excellent	25-30
Good	31-35
Fair-aid not needed	36-40
Passable- may hang up	41-45
Poor-must agitate, vibrate	46-55
Very poor	56-65
Very, very poor	>66

Density analysis: [24]

The volume of powder packing was determined on an apparatus consisting of a graduated cylinder mounted on a mechanical tapping device that has a specially cut rotating cam. An accurately weighed sample of powder was carefully added to the cylinder with the aid of a funnel. Initial volume of powder was noted and the sample subjected to tapping (500, 750 or 1250 tapings) until no further reduction in volume was noted or the percentage of difference in volume was not more than 2 %. A sufficient number of taps should be employed to assure reproducibility for the material in question. The tapings should not produce particle attrition or a change in the particle size distribution of the material being tested.

$$\textbf{Bulk density} = \frac{\text{Weight in gm of sample}}{\text{Volume occupied by sample in ml}} \text{ g/ml} \quad \ldots\ldots\ldots\ldots\ldots\ldots (3)$$

Tapped density:

Tapped density is determined by placing a graduated cylinder containing a known mass of drug on a mechanical tapper apparatus which is operated for fixed number of taps (~ 100) until a powder bed volume has reached the minimum. Using the weight of drug in cylinder and tapped volume, the tapped density is determined.

$$\textbf{Tapped density} = \frac{\text{Weight of powder in gm}}{\text{Tapped volume in ml}} \text{ gm/m l} \quad \ldots\ldots\ldots (4)$$

Compressibility index: [25]

A useful empirical guide is given by Carr's compressibility index.

$$\textbf{Carr's index (\%)} = \frac{\text{Tapped} - \text{Poured density}}{\text{Tapped density}} \text{X } 100 \ldots\ldots\ldots\ldots (5)$$

$$\textbf{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (6)$$

Table.No.10: Scale of flow ability

Compressibility index (%)	Flow character	Hausner ratio
≤10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
> 38	Very, very poor	> 1.60

Table.No.11: Flow properties of Active pharmaceutical ingredient (API)

Flow properties	Lafutidine	Domperidone
Bulk density (gm/ml)	0.4615	0.259
Tapped density (gm/ml)	0.545	0.454
Carr's Compressibility index (%)	18.17	42.85
Hausner ratio	1.18	1.750

The preliminary micromeritic studies carried out on drug suggest that Domperidone posseses very poor flow property. Hence the method of choice for formulation of drug was wet granulation.Once formulated as granules; the flow property of drug was increased**.**

a) Particle size determination:

The procedure involves the electromagnetic sieve shaking of the sample through the series of successively arranged sieves (sieve no. 20, 30, 60, 80 and 100 and receiver), and weighing of the portion of the sample retained on each sieve and calculating percentage retained on each sieve.

Particle size was determined by sieve method.

Weight of sample taken: 50 g.

Table.No.12: Sieve analysis of Lafutidine:

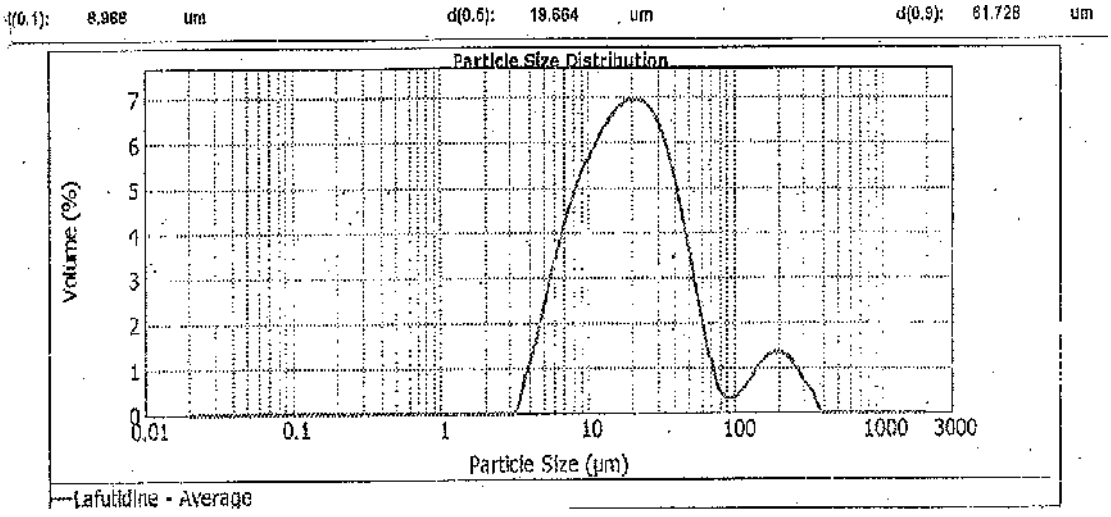
Sieve No.	Qty. retained (g)	Percentage
20 # retained	0.566 g	1.132 %
40 # retained	2.8096 g	5.62 %
60 # retained	0.8822 g	1.7644 %
80 # retained	0.3514 g	0.703 %
100 # retained	0.2628 g	0.5256 %
Fines (Below 100 #)	45.128 g	90.26 %
Total	**50.00 g**	**100.00 %**

Table.No.13: Sieve analysis of Domperidone

Sieve No.	Qty. retained (g)	Percentage
20 # retained	27.678 g	55.35
40 # retained	15.998 g	31.98
60 # retained	3.22 g	6.44
80 # retained	1.14 g	2.28
100 # retained	1.09 g	2.18
Fines (Below 100 #)	1.128 g	2.25
Total	**50.00 g**	**100.00 %**

Particle size analysis of Lafutidine by Malvern

Figure.No.3: Graph showing Particle size distribution by Malvern technique



D (0.9): 61.728 µm (90 % of the particles were 61.728 µm or above)

D (0.5): 19.664 µm (50 % of the particles were 19.664 µm or above)

D (0.1): 6.966 µm (10 % of the particles were 6.966 µm or above)

f) **Moisture content**:

Mositure content studies of API are important as the moisture if absorbed by the drug can play a major role in drug's degradation pathway.

Also the absorbed moisture may sometimes result in the degradation or none functioning of the entire product due to its effect on therapeutic activity of drug and also on the drug excipient incompatibility.

Table.No.14: Hygroscopic criteria as per European Pharmacopoeia

S. No.	**Sample is**	**Criteria as per European Pharmacopoeia** (When Sample is exposed to 80± 2 % RH at 25°C±1°C for 24 hours)
1	Deliquescent	Sufficient water is absorbed to form a liquid
2	Very Hygroscopic	Increase in mass is equal to or greater than 15 %
3	Hygroscopic	Increase in mass is less than 15 % and equal to or greater than 2 %
4	Slightly Hygroscopic	Increase in mass is less than 2 % and equal to or greater than 0.2 %

2. Preparation Of calibration curve of Lafutidine and Domperidone:

Linearity of Lafutidine and Dmperidone was performed using the standard solution in the range of 14.50mcg/ml to 26.93mcg /ml of Lafutidine (ie 70 to 130 % of Standard concentration) and 42.09mcg/ml to 78.17mcg/ml of Domperidone (70 to 130 % of Standard concentration). Standard preparation: Weigh accurately about 20mg Lafutidine working standard and 60mg of Domperidone working standard, transfer into a 100ml volumetric flask, add 70ml of methanol, sonicate to dissolve and make up the volume with methanol.

A graph was plotted with concentration on X axis and mean peak areas on y axis for Lafutidine and Domperidone and correlation coefficient was determined.

Table.No.15: Linearity of Response (Lafutidine)

Sr no	Concentration of Lafutidine in mcg/ml	Mean Peak areas
1	14.50	156611
2	16.57	181679
3	18.64	202751
4	20.71	227669
5	22.78	247176
6	24.85	270177
7	26.93	288577

Standard Curve of Lafutidine.

Figure.4: Standard Curve of Lafutidine.

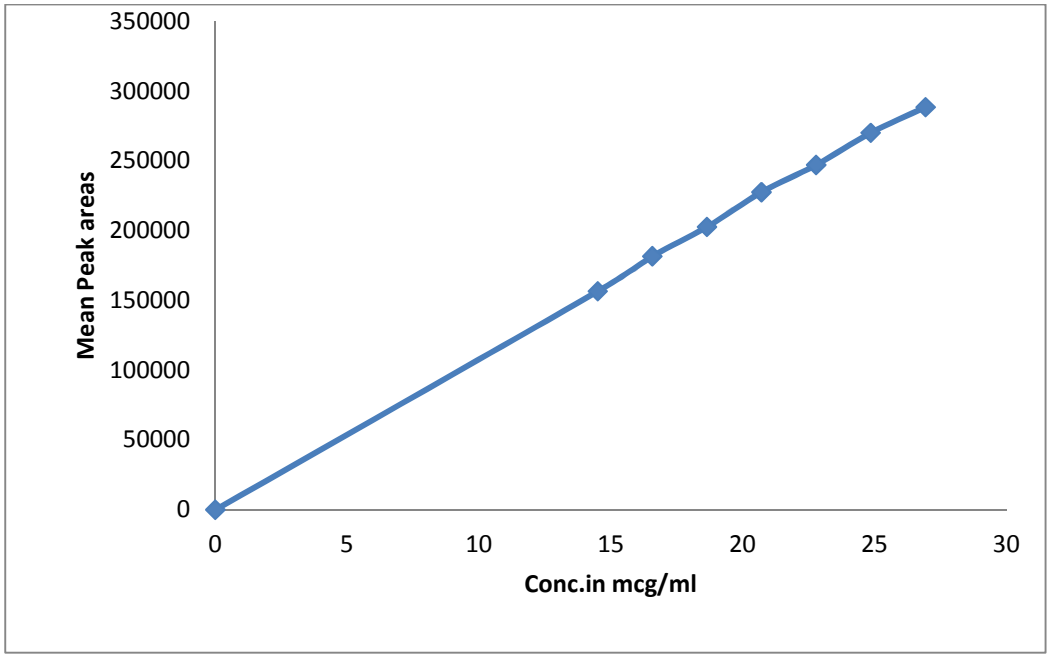
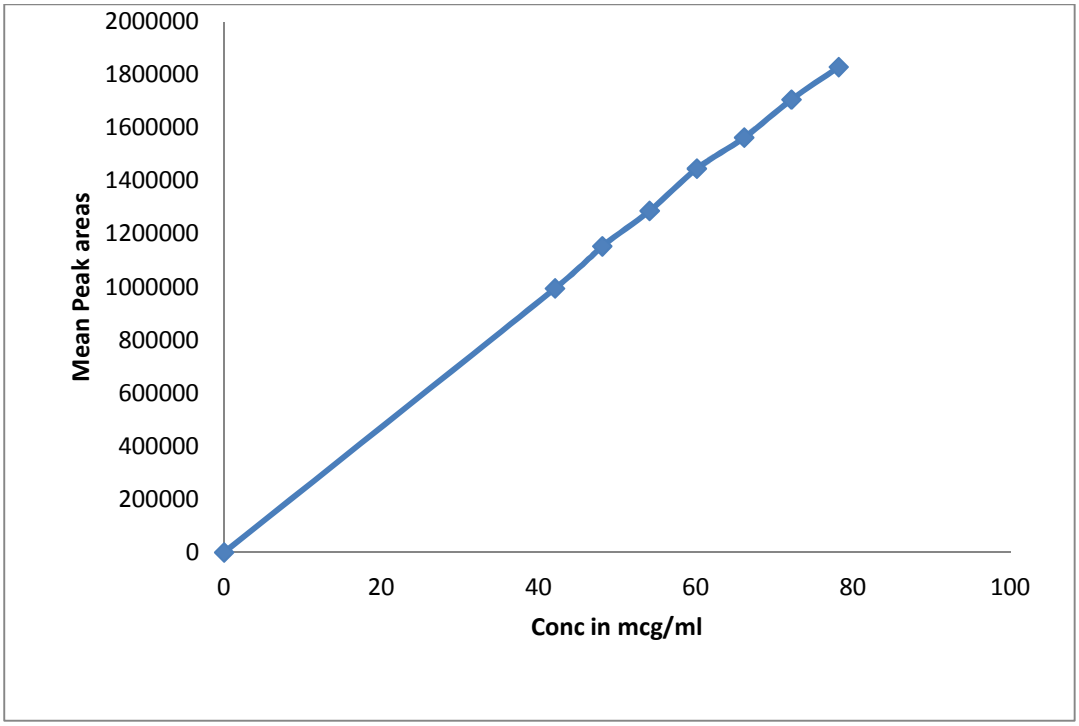


Table.16: Linearity of response (Domperidone)

Sr no	Concentration of Domperidone in mcg/ml	Mean Peak areas
1	42.09	995024
2	48.11	1153687
3	54.12	1287416
4	60.13	1446537
5	66.15	1563481
6	72.16	1706704
7	78.17	1829442

Standard curve of Domperidone

Figure 5: Standard curve of Domperidone



3. **Drug-Excipient Compatibility:**[25]

Knowledge of the interaction of drugs and excipients is essential in the initial formulation of a product. It may also be necessary later on during processing scale-up, when problems arise, to determine if incompatibilities exist which affect manufacturing or stability. Drug-excipient interactions are often directly related to the moisture present in one or another of the components or to the humidity to which the formulation is exposed during processing or storage.

These studies are always carried out at accelerated temperature and humidity conditions, even though it must be recognized that some interactions are physical and not chemical and that accelerated aging may not be predictive. Tests for excipient drug interactions are usually conducted on blends of the pure drug and excipient in ratios similar to those in the final dosage form. For example, excipient to drug ratios are higher for filler-binders than for lubricants and disintegrating agents. These studies are often performed with the help of a factorial or fractional factorial experimental design.[26]

Powders are physically mixed and may be granulated or compacted to accelerate any possible interaction. Samples can be exposed in open pans or sealed in bottles or vials to mimic product packaging. Evaluation of samples includes:

1. Visual inspection for changes in colour or texture.
2. Both HPLC and TLC are commonly employed with unstressed samples being used as controls. In general, only qualitative results are important initially.
3. Differential thermal analysis is applied and the appearance or disappearance of one or more peaks is noted. Isothermal microcalorimetry can also be employed as well as a thermal activity monitor (TAM) technique.

Compatibility studies are essential in characterizing both raw materials and finished formulations. It has been argued that binary drug-excipient screening studies are inefficient, unrealistic, and ignore processing variables. A better approach may be to carefully select potential excipients based on known chemistry and published compatibility data, and perform miniformulation stability studies.[27]

On the basis of Literature survey, Domperidone was found to be compatible with following excipients:

Lactose , Pregelatinised Maize Starch , Microcrystalline Cellulose , Sodium Starch Glycollate Type A , Magnesium Stearate , Titanium dioxide (E171) ,

Hypromellose , Macrogol , Maize starch, microcrystalline cellulose, Povidone, Propylene glycol, silicon dioxide , Polysorbate 20, Lactose monohydrate , Sodium lauryl sulphate, Silica colloidal anhydrous .[29]

On the basis of Literature survey, Lafutidine was found to be compatible with following excipients:

Lactose, microcrystalline cellulose, corn starch, light anhydrous silica , croscarmellose sodium, hydroxypropylcellulose, talc, magnesium stearate, hydroxypropyl methylcellulose 2910, macrogol 6000, titanium oxide, and carnauba wax .[28]

The drug excipient compatibility study was carried out by following two methods:

1) Accelerated stability condition.
2) DSC studies.

The drug and individual excipient mixture of all excipients were taken in the ratio given in tables below. The prepared composition was passed through 30# sieve for uniform mixing of the composition. 3gm of the mixture was filled in 10ml clear glass vials. The two methods employed are open vial and closed vial with HDPE stopper. The samples were observed for physical changes in 15 days and 1 Month duration.

Differential scanning calorimetry or DSC is a thermo analytical technique in which the difference in the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature. Both the sample and reference are maintained at nearly the same temperature throughout the experiment. Generally, the temperature program for a DSC analysis is designed such that the sample holder temperature increases linearly as a function of time. The reference sample should have a well-defined heat capacity over the range of temperatures to be scanned.

The result of a DSC experiment is a curve of heat flux versus temperature or versus time. The melting point of Lafutidine is 96-99°and that of Domperidone is 244-248°C.

4. Analytical method:

4.1 Assay by HPLC: Determination of content of Lafutidine and Domperidone.

Preparation of 6.8 phosphate buffer solution:

Dissolve 4.45g of disodium hydrogen phosphate dihyadrate ($Na_2HPO_4,2H_2O$) in 1000ml of water. Adjust pH to 6.5 with orthophosphoric acid.

Preparation of mobile phase: Prepare a mixture of pH 6.8 phosphate buffer solution and Acetonitrile in ratio of 70:30.Filter and degas.

Standard preparation:

Weigh accurately about 20mg Lafutidine working standard and 60mg of Domperidone working standard , transfer into a 100ml volumetric flask, add 70ml of methanol, sonicate to dissolve and make up the volume with methanol. Further dilute 5ml to 50ml with mobile phase.

Assay preparation:

Weigh and transfer the content of 20 capsules and powder the content. Weigh accurately quantity of powder containing the equivalent of about 30mg of Domperidone into a 100ml volumetric flask. Add 70ml of methanol sonicate for 15minutes with intermittent shaking and make up the volume with methanol. Filter through 0.45µ Nylon membrane filter or 0.45µ PVDF membrane filter. Further dilute 5ml to 25ml mobile phase.

Chromatographic conditions:

Column: Octadecylsilane column, 250 mm X 4.6mm, 5µ (XTerra or equivalent)

Flow rate: 1.0ml/ min

Wavelength: 276nm

Injection volume: 20µl

Column Temperature: 30ºC

Run time: 30 minutes

Procedure:

Wash the column and equilibrate with mobile phase. Seperately inject equal volumes (20µl) of standard preparation (five replicate injections) and assay preparation (Duplicate injection) into the chromatograph. The system suitability

parameters should be met. From the peak responses, calculate the content of Domperidone and Lafutidine in the sample.

Calculation:

Content of Lafutidine

% Content of Lafutidine = $\frac{A_T \times W_{std} \times 5 \times 100 \times 25 \times P \times \text{Avg filled weight}}{A_s \quad 100 \quad 50 \quad W_{test} \quad 5 \quad 100 \quad L.C} \times 100$

A_T = Average of the area counts of the Lafutidine peak obtained from the chromatograms of the assay preparation.

A_s = Average of the area of the Lafutidine peak obtained from the chromatograms of the standard preparation.

W_{std} = Weight of the Lafutidine working standard taken in mg.

W_{test} = Weight of sample taken in mg.

P = % Potency of Lafutidine working standard.

L.C= Label claim of Lafutidine in mg.

Content of Domperidone

% Content of Domperidone= $\frac{A_T \times W_{std} \times 5 \times 100 \times 25 \times P \times \text{Avg filled weight}}{A_s \quad 100 \quad 50 \quad W_{test} \quad 5 \quad 100 \quad L.C} \times 100$

A_T = Average of the area counts of the Domperidone peak obtained from the chromatograms of the assay preparation.

A_s = Average of the area of the Domperidone peak obtained from the chromatograms of the standard preparation.

W_{std} = Weight of the Domperidone working standard taken in mg.

W_{test} = Weight of sample taken in mg.

P = % Potency of Domperidone working standard.

L.C= Label claim of Domperidone in mg.

4.2 Dissolution Method

Following method was applied through out the dissolution study of the product.

Dissolution was carried out initially in 0.1N HCL for 2hrs followed by 6.8 phosphate buffer for 24hrs.

4.2.1 Dissolution in acidic media (0.1N HCL)

Table 17: Dissolution Parameters

Dissolution medium	0.1 N HCl
Dissolution medium volume	900 ml
Apparatus	USP - 2 (paddle)
Speed	100rpm
Temperature	37±5^{o}C
Sampling time interval	30mins,1hr, 2hr

Standard preparation

Weigh accurately about 77mg of Domperidone maleate working standard and 20mg of Lafutidine working standard into a 100ml volumetric flask, add 80ml methanol.Sonicate to dissolve and make up the volume with methanol. Further dilute 5ml of this solution to 100ml with dissolution media.

Test preparation

Transfer 900ml of dissolution medium in the vessel carefully and allow equilibrating to a temperature of 37±0.5ºC. Place one capsule in each of the vessels and operate the apparatus at 100 rpm. Withdraw 10ml of the sample from each of the dissolution vessel at given time point and filter through 0.45µ membrane filter.

Note: After completion of dissolution in (0.1 N HCl, acidic medium) (2 hrs), carefully remove the dissolution medium without disturbing the capsules. Use the same capsules for further dissolution in phosphate buffer pH 6.8.

Procedure

Wash the column and equilibrate with mobile phase. Seperately inject equal volumes of the standard preparation (five replicate injections) and test preparation (singe injection) into the chromatograph. Record the chromatograms and measure the peak responses for Lafutidine and Domperidone. The system suitability parameters should be met. From peak responses, calculate the content of Lafutidine and Domperidone in the sample.

Table 18: component Retention time

Sr no	Component name	Retention time
1	Lafutidine	7.0 minutes
2	Domperidone	15.0 minutes

Calculation

% Domperidone released = $\frac{A_T \times W_{std} \times 5 \times 900 \times P \times 100}{A_s \quad 100 \quad 100 \quad 1 \quad 100} \times F$ L.C

Where,

A_T = Area counts of the Domperidone peak obtained from the chromatograms of the test preparation.

A_s = Average of the area of the Domperidone peak obtained from the chromatograms of the standard preparation.

W_{std} = Weight of the Domperidone working standard taken in mg.

P = % Potency of Domperidone working standard.

L.C= Label claim of Domperidone in mg/tab.

F= Conversion factor of Domperidone maleate to Domperidone 0.7858.

Correction factor= % Domperidone released (uncorrected) x volume of dissolution media sampled or replaced / total volume of dissolution media.

% Domperidone released (corrected) (in 0.1N Hydrochloric acid stage)= % Domperidone released (uncorrected) + sum of correction factor of all previous intervals.

% Lafutidine released = $\frac{A_T \times W_{std} \times 5 \times 900 \times P}{A_s \quad 100 \quad 100 \quad 1 \quad 100} \times$ L.C

Where,

A_T = Area counts of the Lafutidine peak obtained from the chromatograms of the test preparation.

A_s = Average of the area of the Lafutidine peak obtained from the chromatograms of the standard preparation.

W_{std} = Weight of the Lafutidine working standard taken in mg.

P = % Potency of Lafutidine working standard.

L.C= Label claim of Lafutidine in mg/tab.

Correction factor= % Lafutidine released (uncorrected) x volume of dissolution media sampled or replaced / total volume of dissolution media.

% Lafutidine released (corrected) (in 0.1N Hydrochloric acid stage)= % Lafutidine released (uncorrected) + sum of correction factor of all previous intervals.

3.2.2 Dissolution in Phosphate Buffer pH 6.8

Table 19: Dissolution Parameters

Dissolution Medium	Phosphate buffer pH 6.8 (900ml)
Apparatus	USP type II
Speed	100 rpm
Time	2,4,6,8,10,12,14,16,18 hrs
Temperature	37±5 ºC

Preparation of Phosphate buffer pH 6.8

Dissolve 68 gm of Potassium dihydrogen phosphate in10000 ml of water and adjust the pH to 6.8 with 10%w/w sodium hydroxide solution.

Standard preparation

Weigh accurately about 77g of Domperidone maleate working standard and allow the medium to equilibrate to temperature of 37± 5º C. All the six capsules of acid dissolution medium continue in pH 6.8 phosphate buffer, place one capsule in each of the vessels and operate the apparatus at 100 rpm. Withdraw 10ml of the sample from each dissolution vessel and filter through 10µ membrane filter of

instrument or withdraw 10ml of the sample manually from each dissolution vessel at given time interval and filter through 0.45µ membrane filter.

Procedure

Wash the column and equilibrate with mobile phase.Seperately inject equal volumes (20µl) of the standard preparation (five replicate injections) and test preparation (single injection) into chromatograph .Record the chromatograms and measure the peak responses for Domperidone. The system suitability parameters should be met. From the peak responses, calculate the content of Domperidone in sample.

Calculation

% Domperidone released = $\frac{A_T \times W_{std} \times 5 \times 900 \times P \times 100}{A_s \quad 100 \quad 100 \quad 1 \quad 100 \quad L.C} X\ F$

Where,

A_T = Area counts of the Domperidone peak obtained from the chromatograms of the test preparation.

A_s = Average of the area of the Domperidone peak obtained from the chromatograms of the standard preparation.

W_{std} = Weight of the Domperidone working standard taken in mg.

P = % Potency of Domperidone working standard.

L.C= Label claim of Domperidone in mg/tab.

F= Conversion factor of Domperidone maleate to Domperidone 0.7858.

Correction factor= % Domperidone released (uncorrected) x volume of dissolution media sampled or replaced / total volume of dissolution media.

% Domperidone released (corrected) (in 0.1N Hydrochloric acid stage)= % Domperidone released (uncorrected) + sum of correction factor of all previous intervals.

% Total Domperidone released = % Domperidone released (corrected in acid stage) + % Domperidone released (corrected) (in pH 6.8 phosphate buffer stage).

5. Formulation and development

5.1) Materials

The active pharmaceutical ingredient (API) , the excipients and coating material used for the development of the product are given in following table.

Table 20: Materials used for the Product development

Sr. No.	Name	Suppliers of Material
1	Domperidone	Vasudha Pharma.
2	Lafutidine	Optimus Pharma Ltd.
3	Methocel K4M	Indchemie Health specialities pvt ltd.
4	HPMC 15 cps	Vasudha Pharma.
5	Povidone K-30	Alkem Laboratories Ltd.
6	Colloidal anhydrous silica	Cabot Sannar Ltd.
7	Microcrystaline cellulose (Avicel PH 102)	Sigachi Chloro Chemicals ltd.
8	Lactose DCL	Optimus Pharma Ltd.
9	Pregelatinised Maize starch	Cabot Sannar Ltd.
10	Citric acid monohydrate	Alkem Laboratories Ltd.
11	Crosscarmellose sodium (Ac-di-Sol)	Optimus Pharma Ltd.
12	Magnesium stearate	Amishi Drug & Chemical .
13	Isopropyl alcohol	Merck.
14	Purified water	Alkem Laboratories Ltd.
15	Instacoat A05D00512	Ideal Cures Ltd.
16	Isopropyl alcohol	Merck.
17	Methylene chloride	Rankem (Ranbaxy Ltd).

Coating material (product code number) contains: Talc, HPMC E-5, indigo carmine, PEG 6000.

5.2) Equipments used:

Table 21: list of equipments used

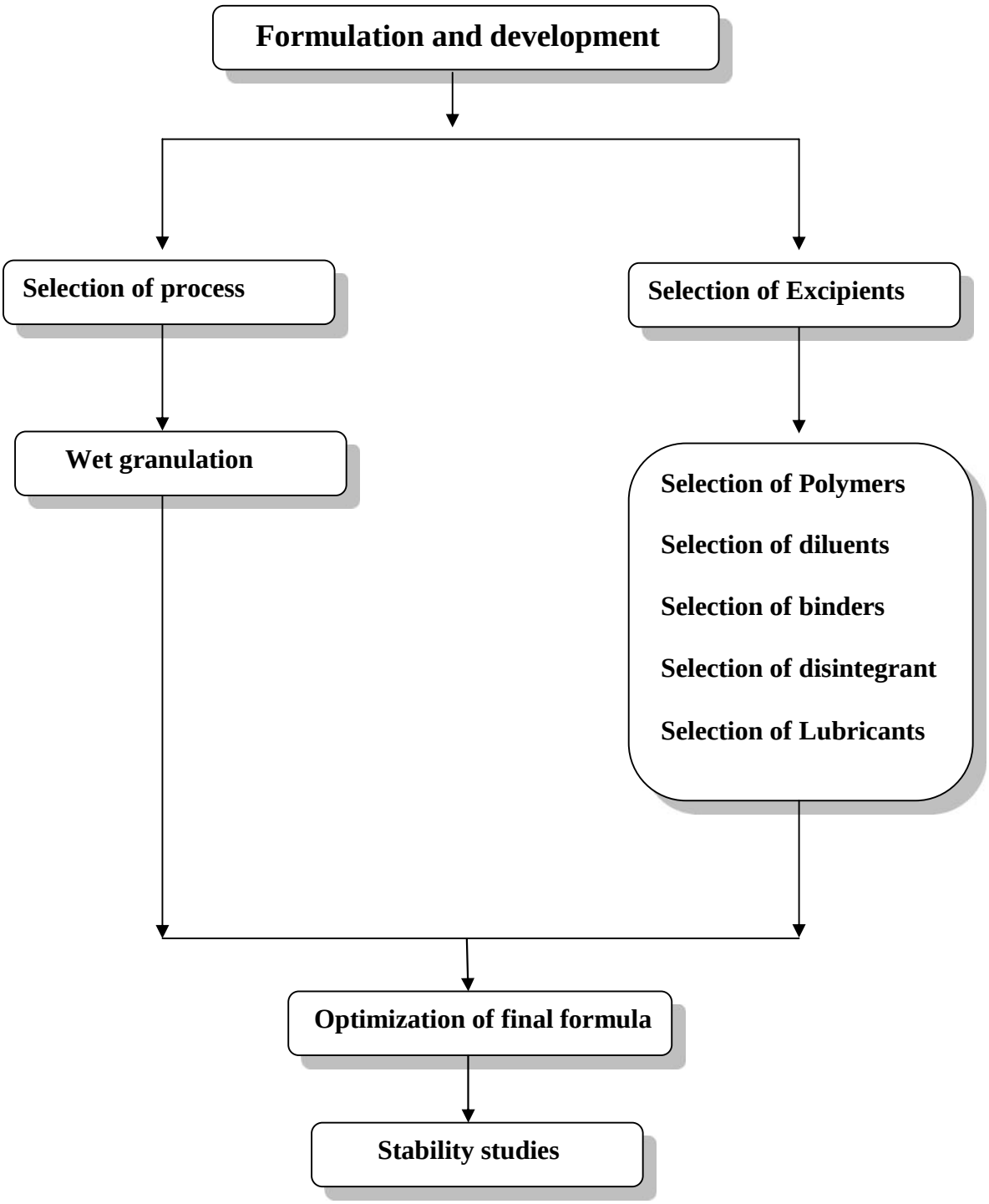
Sl. No.	Equipments	Manufacturer
1	Tablet compression machine	Cadmach (16 station, single rotary, compression machine, with 'D' tooling setup)
2	Punch Set (6.5 X 6.5 SC, plain on both sides)	Parle Global Punching tools Pvt. Ltd.
3	Tablet coating machine	Pharma R&D Coater
4	Rapid mixing granulator (RMG)	Kevin
5	Dissolution apparatus	Electrolab (TDT-08L)
6	HPLC apparatus	Dionex (P-680),Waters (2695), Agilent (1100)
7	UV-Visible spectrophotometer	Jasco V 530 & Perkin Elmer (Lambda25)
8	Differential scanning calorimeter	Mettler Toledo (DSC-822^e)
9	Rapid dryer	Retsch (TG-100)
10	Electromagnetic sieve shaker	Electrolab (EMS-8)
11	Loss on drying apparatus	Mettler Toledo (HB 43)
12	Capsule Filling machine (semi automatic)	Pam Glatt
13	Hardness tester	Monsanto Hardness Tester
15	Density apparatus	Electrolab (ETD-1020)
16	Blender	Pretime – D
17	Mechanical shaker	Skan
18	Roche friabilator USP	Electrolab (EF-1W)
19	Vernier caliper	Mitutoyo (absolute digimatic)
20	Digital pH meter	Lab india
21	Digital weighing balance	Mettler Toledo (AB 204-S)

The sustained release Tablet of Domperidone is not official in any of the Pharmacopoeia; hence the present product development strategy was aimed by developing a tentative specification for 24 hrs release, based on the pharmacokinetic parameters as well as the results obtained from few of the trial batches. The release profile decided is as follows:

Table 22:: Tentative Release profile

Time (In Hours)	**% Domperidone Release**
2nd Hour	30-40%
4th Hour	40-60%
8th Hour	NLT 60%
12th Hour	60-70%
18th Hour	70-85%
24th Hour	NLT 85%

The formulation work was carried out as follows



5.3) Formulation Methods

5.3.1) Formulation of Lafutidine blend

Table 23: Formulation of Lafutidine blend

Sr no	Ingredients	Batch 001 Qty (mg/capsule)	Batch 002 Qty (mg/capsule)	Batch003 Qty (mg/ capsule)
1	Lafutidine	10.04	10.04	10.04
2	Lactose DCL 21	129.50	129.5	127.46
3	Microcrystalline Cellulose (MCC PH 102)	98.46	98.46	100
4	Crosscarmellose sodium (Ac-Di-Sol)	-	10	10
5	Sodium starch glycollate (SSG)	10	-	-
6	Colloidal Silicon Dioxide (Aerosil-200)	1	1	1.5
7	Magnesium stearate	1	1	1
Total weight (mg)		250	250	250

Steps involved in the formulation of Lafutidine blend are as follows:

1) Sifting

Weighed quantity of Lafutidine, Lactose DCL 21, Microcrystalline cellulose pH 101, Crosscarmellose sodium was passed through 30 # sieve.

2) Dry blending

The materials of step 1 were mixed together in double cone blender for 10 minutes and were again passed through 30# sieve.

3) Prelubrication

Weighed quantity of Aerosil 200 was passed through 30 # sieve and was added to material of step 2 and mixed in the blender for 15 minutes.

4) Lubrication

Weighed quantity of Mg stearate was passed through 60# sieve and was added to material of step no 6 in the blender and further mixing was carried out for 5 minutes.

5.3.2) Formulation of Domperidone IR tablets:

Table 24 Formulation of Domperidone IR tablets.

Sr No	Ingredient	Batch 001 Qty (mg/tab)	Batch 002 Qty (mg/tab)	Batch 003 Qty (mg/tab)
1	Domperidone	10.06	10.06	10.06
2	Lactose Monohydrate	41	35	40
3	Microcrystalline Cellulose (PH 101)	20.04	16.94	16.94
4	Maize Starch	5	15	10
5	Polyvinyl pyrollidone (PVP K 30)	3	1	1
6	Pregelatinised Maize starch	10	0	0
7	Sodium Starch glycollate (SSG)	0	11	11
8	Colloidal silicon dioxide (Aerosil 200)	0.45	0.5	0.5
9	Magnesium stearate	0.45	0.5	0.5
10	Purified Water	40ml	40ml	40ml
Total weight(mg)		90	90	90

Steps involved in the formulation of Domperidone IR tablets are as follows:

1) **Sifting**

   Weighed quantity of Domperidone, Lactose Monohydrate and Microcrystalline cellulose pH 101 was passed through 30 # sieve.

2) **Dry mixing**

   The materials of step 1 were mixed together in RMG for 10 minutes and were again passed through 30# sieve.

3) **Granulation**

- **Binder preparation**: Dissolve Polyvinyl Pyrollidone K-30 in purified water. Take weighed amount of Starch and Transfer it into the above S.S. vessel and make uniform slurry. Filter it through muslin cloth. Boil Purified Water in a Stainless steel container.Transfer the filtered slurry of starch and PVPK-30 gradually under constant stirring to the container. Stir for enough time to get homogenous, translucent paste. Cool the Paste to 50-60°C.
- **Kneading**: The binder solution prepared in above step was added to the dry mix of step 2 while operations the RMG at a slow speed to get dough mass. Additional water was added to achieve the desired granulation point if the dough mass formed was not proper and the total quantity of water was noted down.

  Chopper was used for a period of 1 minute if the dough mass formed contained sufficient quantityof lumps.
- **Wet screening:**

  The wet mass of above step was passed through 20# sieve.
- **Drying:** The wet granules obtained in the above step were dried in tray drier at a temperature of about 50-55 º C (with raking after every 10 minutes). The granules were dried till the desired LOD was obtained ie about 3% w/w. The drying time was noted down during this step.
- **Rasping:** (Dry screening):

  The dried granules were passed through 20 # sieve.

4) **Prelubrication**:

   SSG and Aerosil 200 were passed through 30 # screen and were added to the dried granules obtained in the above step and mixed for 10 minutes in blender.

5) Lubrication:

Weighed amount of Magnesium stearate was passed through 60 # sieve and was added to granules obtained in the above step and mixed in the blender for 5 minutes.

6) Compression:

The compression operation was carried on Rotary Tablet Compression Machine fitted with 6. 5 mm round shaped, standard concave punch sets having plain on both sides at average weight 90.0 mg/tab.

5.3.3) Formulation of Domperidone SR tablets:

Table 25 Formulation of Domperidone SR tablets

Sr No	Ingredient	Batch 001 Qty (mg/tab)	Batch 002 Qty (mg/tab)	Batch 003 Qty (mg/tab)	Batch 004 Qty (mg/tab)
1	Domperidone	20.11	20.11	20.11	20.11
2	Lactose Monohydrate	76.89	76.89	49.39	44.09
3	HPMC K4M	26	25	12	12
4	HPMC 15 cps	-	-	30	30
5	Polyvinyl Pyrrolidone (PVP K 30)	3	5	5	5
6	Isopropyl alcohol	80ml	80ml	70ml	80ml
7	Citric Acid monohydrate	-	1.2	12	18
8	Colloidal silicon dioxide (Aerosil 200)	2	1	0.5	0.5
9	Magnesium stearate	2	1	1	0.5
Total weight (mg)		130	130	130	130

Steps involved in the formulation of Domperidone SR tablets are as follows:

1. **Sifting:**

   Weighed quantity of Domperidone, Lactose Monohydrate and Methocel K4M was passed through 30 # sieve.

2. **Dry mixing:**

   The materials of step 1 were mixed together in RMG for 10 minutes at slow speed and were again passed through 30# sieve.

3. **Granulation**:

- **Preparation of Binder**:

  Weighed amount of PVP-K-30 was transfered into a S.S. vessel containing Isopropyl alcohol and was stirred to get a clear solution.

- **Kneading:**

  The binder solution prepared in above step was added to the dry mix of step 2 while operation the RMG at a slow speed to get a dough mass. Additional IPA was added to achieve the desired granulation point if the dough mass formed was not proper and the total quantity of water was noted down.

  Chopper was used for a period of 1 minute if the dough mass formed contained sufficient quantity of lumps.

- **Wet screening**:

  Pass the wet mass of above step through 20# Screen.

- **Drying:**

  Dry the wet granules of above step in tray drier at temperature 40-45°C (with raking after 10 minutes) (approx 30 minutes). Dry the granules till LOD is NMT 3.0% w/w. Note the drying temperature and time required .

- **Rasping** (Dry screening):

  The dried granules obtained in above step were passed through 20# sieve.

4. **Prelubrication:**

   Aerosil 200 was passed through 30 # screen and was added to the dried granules obtained in the above step and mixed for 10 minutes in blender.

5. Lubrication:

Mg stearate was passed through 60 # sieve and was added to the above step and mixed for 5 minutes in blender.

6. Compression:

Compression operation was carried on Rotary Tablet Compression Machine fitted with 6.5 mm round shaped, standard concave punch sets (D tooling) having plain on both sides at average weight 130.0 mg/tab.

7. Coating:

- **Preparation of Coating solution**:

Isopropyl alcohol was taken in a S.S container fitted with a strrier having variable speed regulator. Slowly Instacoat universal blue (A05D00511) was added into it stirring continously for 30 minutes.

The coating dispersion was filtered through muslin cloth into another tank fitted with stirrer

.

- **Coating procedure:**

Dedusted tablets were charged in the coating pan and preheated to about 45^{o}C.When exhaust temperature reached 30-40^{o}C, coating dispersion was sprayed continuously onto rolling tablet bed at a speed of 1-2 rpm. Tablets were intermittently checked for quality of coat and weight gain.

After completion of the coating, tablets were dried in the coating pan at inlet temperature between 30-40^{o}C for a period of 10 minutes.

5.3.4) Capsule Filling:

The prepared Lafutidine blend, Domperidone IR tablets and Domperidone SR tablets were filled in the Size '0' Capsule.

The capsules were filled using semi automatic capsule filling machine. Individual Domperidone IR tablets and Domperidone SR tablets were filled into each of the capsule manually. Weighed amount of Lafutidine blend was further placed in the capsule.

Table 26: Ingredient weights

Sr. No.	Ingredient	Qty mg / Capsules	Category
1.	Lafutidine Blend	250.000	Powder
2	Domperidone IR Tablets	90.000	Tablets
3.	Domperidone SR tablets	135.000	Tablets
4.	E.H.G. Capsules Size "0"	91.0	Capsule Shell

RESULT AND DISCUSSION

1. Preformulation Study

The preformulation study was carried out by studying various aspects of characteristics of API as well as by compatibility study.

Preformulatin study consists of

- Pre-compresson Parameters.
- Post-compression Parameters.

This includes Loss on Drying of dried granules and final blend, bulk density, tapped density, Carr's Index, Hausner's Ratio and sieve analysis in pre-compression parameters and average weight, thickness, hardness, disintegration time, friability, and in-vitro dissolution in post-compression parameters

Pre-Compression Parameters:

In process Parameters of Lafutidine Blend:

Table 27: Parameters of Lafutidine Blend

Sr No	Parameters	Batch 001	Batch 002	Batch 003
1	Bulk Density (gm/ml)	0.505	0.530	0.1513
2	Tapped Density (gm/ml)	0.69	0.78	0.699
3	Hausner ratio	1.366	1.344	1.272
4	Carr's Compressibility Index (%)	26.81	26.4	22.72

Assay (% Drug content)

Table 28: percentage of drug content

Batch 001	Batch 002	Batch 003
99.00	98.90	99.3

In process parameters of Domperidone IR granules:

Table 29: parameters of Domperidone IR granules

Sr No	Parameters	Batch 001	Batch 002	Batch 003
1	Bulk Density (gm/ml)	0.559	0.561	0.471
2	Tapped Density (gm/ml)	0.673	0.666	0.581
3	Hausner Ratio	1.204	1.187	1.23
4	Carr's Compressibility Index (%)	16.94	15.87	18.86
5	LOD Of granules (% w/w)	2.08	2.27	2.07

Assay (% Drug content)

Table 30: percentage of drug content

Batch No 001	Batch No 002	Batch No 003
101.3	98.70	99

In Process Parameters of Domperidone SR granules

Table 31: Parameters of Domperidone SR granules

Sr no	Parameter	Batch No 001	Batch No 002	Batch No 003	Batch No 004
Tablets compressed using 6.5mm standard concave punch Plain on both sides					
1	Bulk Density (gm/ml)	0.545	0.521	0.453	0.567
2	Tapped Density (gm/ml)	0.598	0.634	0.598	0.674
3	Hausner ratio	1.097	1.21	1.32	1.188
4	Carr's compressibility index (%)	8.86	17.82	24.24	15.87
5	LOD (%w/w)	2.07 %	2.32%	2.17%	2.00%

1.1. Pre-Compression Parameters

a) Loss on Drying (LOD)

Moisture content of Domperidone IR granules was kept between 2.0 to 2.05% w/w.

Moisture content of Domperidone SR granules was kept between 2.0 to 2.05% w/w.

b) Blend Flow Characteristics

The flow property of API i.e. Domperidone indicate that it posseses erratic flow characteristics. Hence the method was choice was wet granulation method.

Flow Properties of Domperidone IR granules

- Bulk density in the range 0.49- 0.55 gm/ml.
- Tapped density in the range 0.58-0.67 gm/ml.
- Carr's Index ranging 15.6-18%.
- Hausner's ratio in the range 2.07-2.5 shows the good flow characteristics.

Flow Properties of Domperidone SR granules

- Bulk density in the range 0.52-0.6 gm/ml.
- Tapped density in the range 0.59-0.67 gm/ml.
- Carr's Index ranging 8-15.
- Hausner's ratio 1.09-1.2 in the range shows the good flow characteristics.

- **Post-Compression Parameters**

In process Parameters of Domperidone SR granules

Table 32: Parameters of Domperidone SR granules

Sr no	Parameter	Batch no 001	Batch no 002	Batch no 003
Tablets were compressed using 6.5 mm standard concave punch plain on both sides				
1	Avg weight (mg) (20 tablets)	90.8	90.90	90.2
2	Thickness (mm)	2.80	2.75	2.82
3	Hardness (N)	40	50	38
4	Friability (% w/w)	0.01	0.1	0.1
5	Disintegration time (minutes)	4	3	1

In Process Parameters of Domperidone SR uncoated tablets

Table 33: Parameters of Domperidone SR uncoated tablets

Sr No	Parameters	Batch No 001	Batch No 002	Batch No 003	Batch No 004
Tablets were compressed using 6.5mm standard concave punch plain on both sides.					
1	Average weight (mg) (20 Tablets)	130.5	129.6	128	127.5
2	Hardness (N)	115	128	125	131
3	Thickness (mm)	3.60	3.30	3.48	3.53

In Process Parameters of Domperidone SR coated tablets

Table 34: Parameters of Domperidone SR coated tablets

Sr No	Parameters	Batch 01	Batch 02	Batch 03	Batch 04
Tablets were compressed using 6.5mm standard concave punch plain on both sides.					
1	Avg weight (mg) (20 tablets)	133.5	134.2	132	133.2
2	Hardness (N)	120	132	130	135
3	Thickness (mm)	3.72	3.50	3.60	3.64
4	Assay	103.2%	100.5%	102.9%	101%

1.2. Post Compression Parameters:

a. **Weight Variation:** There was no weight variation observed for Domperidone IR as well as Domperidone SR tablets. Weight variation observed in the final capsule was within limit.

b. **Thickness Evaluation:** Thickness of tablets was observed by using Vernier Caliper. Thickness of both the tablets does not show any measurable deviation.

c. **Hardness Test:** Hardness of the tablet was measured in 'Newton' unit in digital hardness tester. The hardness of Domperidone IR tablets was found to be between 45-50 Newton.

The hardness of Domperidone SR uncoated tablets was found to be between 120-130 N and that of coated tablets was found to be between 130-135 Newton.

d. **Friability Test:** The friability was carried out by using Roche Friabilator. The percentage friability of tablet was ranging 0.01% - 0.1%; 0.010% - 0.030% for Domperidone IR and SR tablets. They are less than the standard limit of 1% indicates that the prepared tablets are mechanically stable.

2 .COMPATIBILITY STUDY

Drug–Excipient compatibility study of Lafutidine with Domperidone capsule was carried out with different excipients .The study was carried out at different conditions of temperature and humidity like 40°C/75%RH, 2–8°C, room temperature & was observed for their physical appearance and assay after 2 week, 4 weeks and was compared with the initial value.

Compatibility studies between Lafutidine and Domperidone with excipients by Differential scanning calorimetry (DSC).

DSC thermograms of pure drugs Lafutidine and Domperidone is shown below:

Figure 6: DSC thermograph of Lafutidine (Initial)

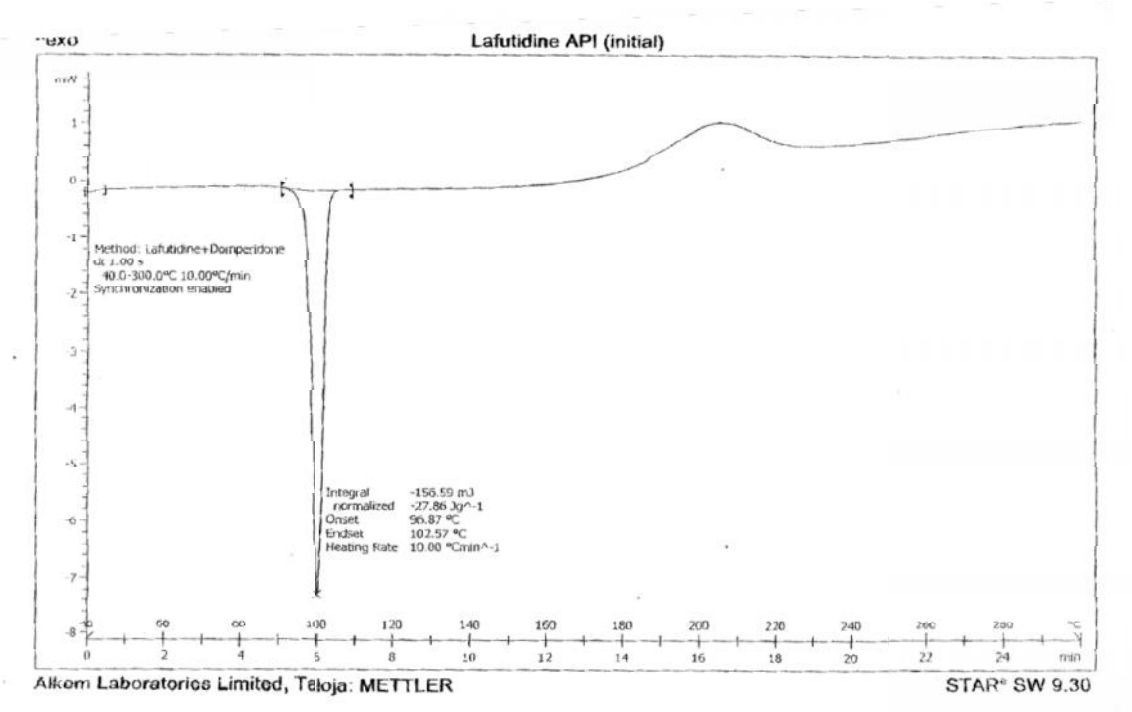


Figure 7: DSC thermograph of Lafutidine API 1M (40ºC/75%RH)

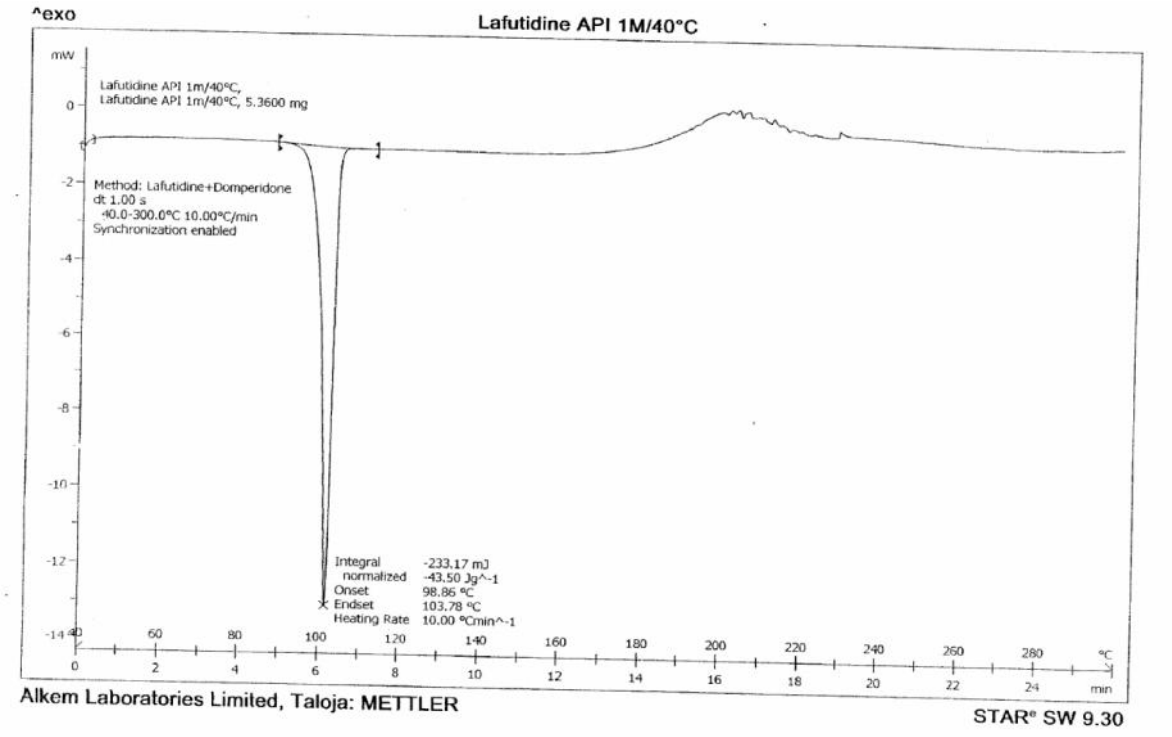


Figure 8: DSC thermograph of Domperidone (Initial)

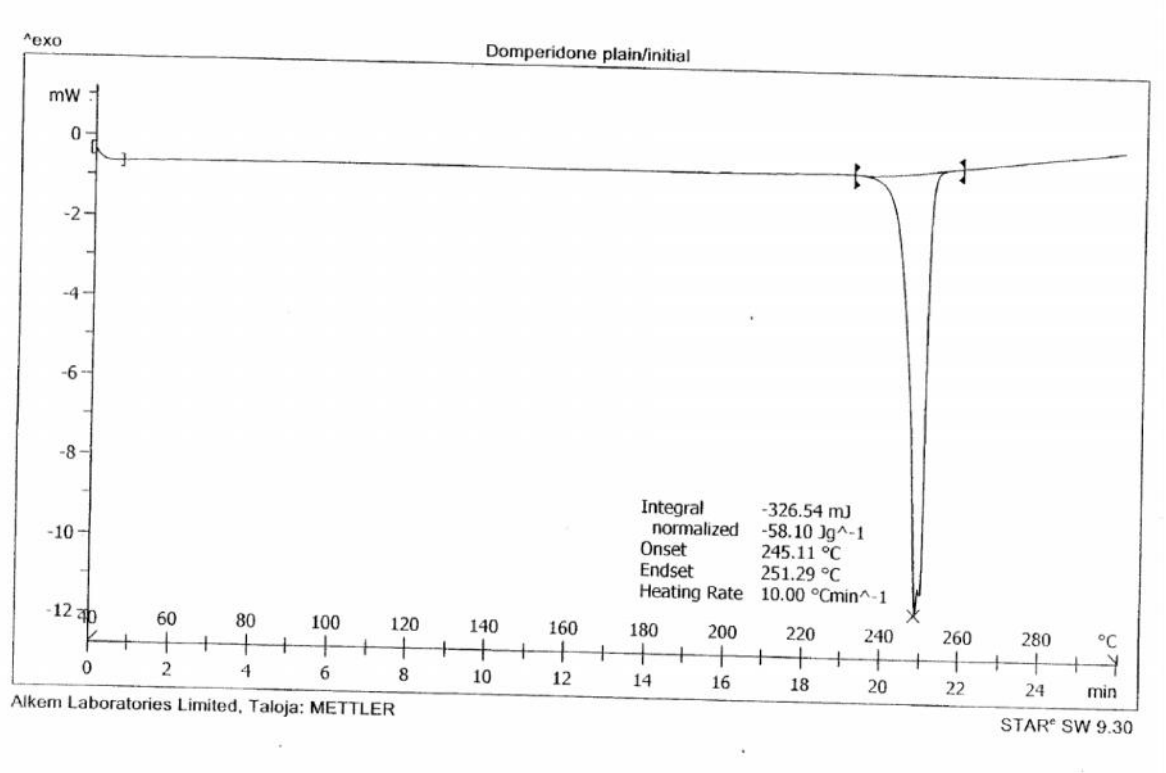


Figure 9: DSC thermograph Of Lafutidine plus Domperidone (Initial)

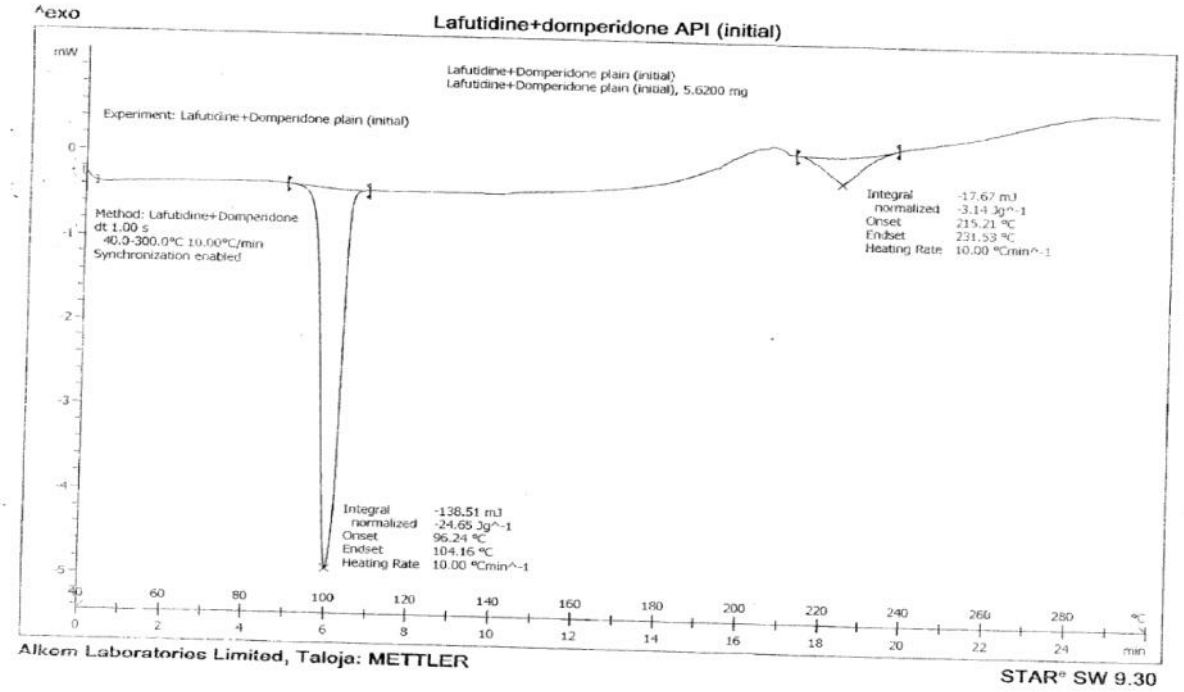


Figure 10: DSC thermograph of Domperidone API 1M (40ºC/ 75 % RH)

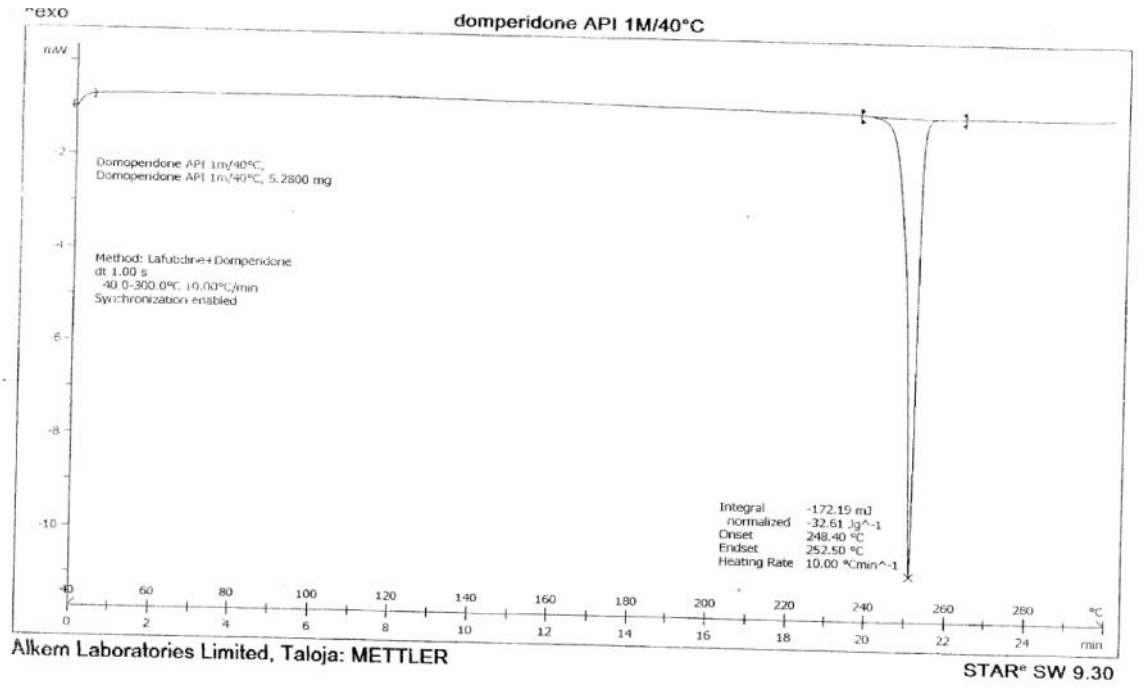


Figure10: DSC thermogram of Lafutidine plus Domperidone API 1M

(40ºC/ 75 % RH)

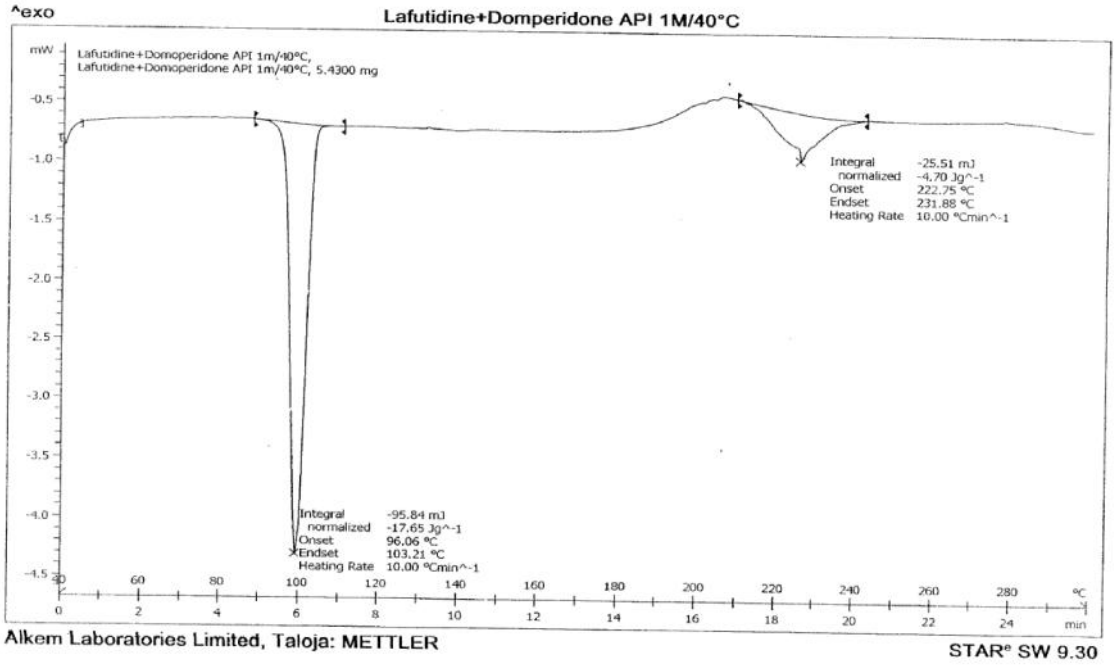


Figure 11: DSC thermogram of Lafutidine plus Domperidone Capsule (Placebo) Initial

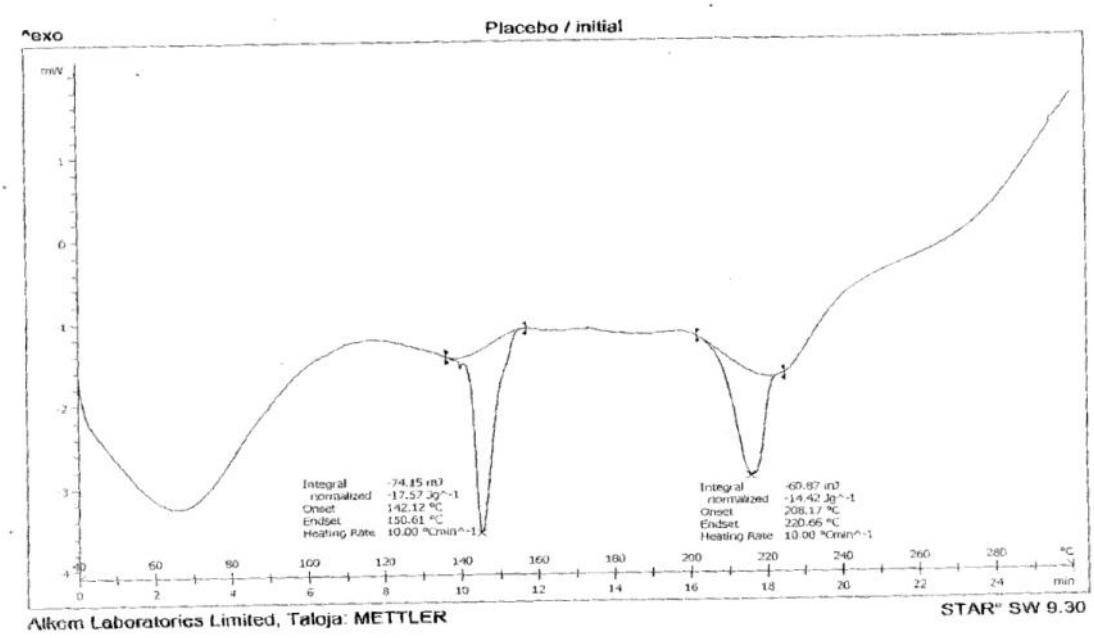


Figure 12: DSC thermogram of Lafutidine plus Domperidone 1M (40ºC/75% RH)

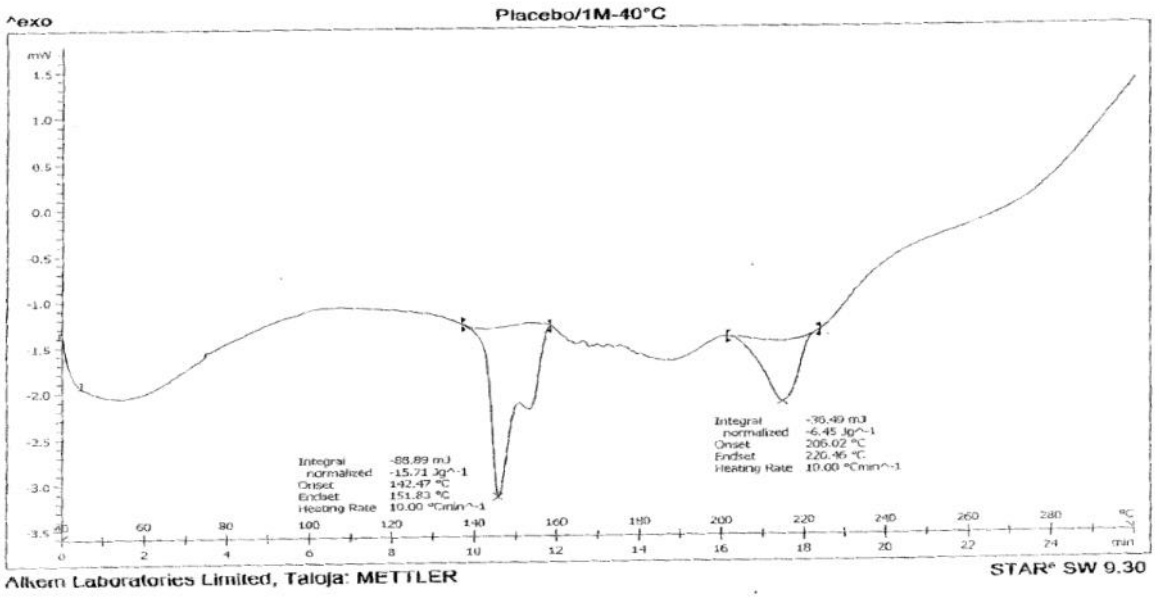


Figure 13: DSC thermogram of Lafutidine plus Domperidone Capsule (Initial)

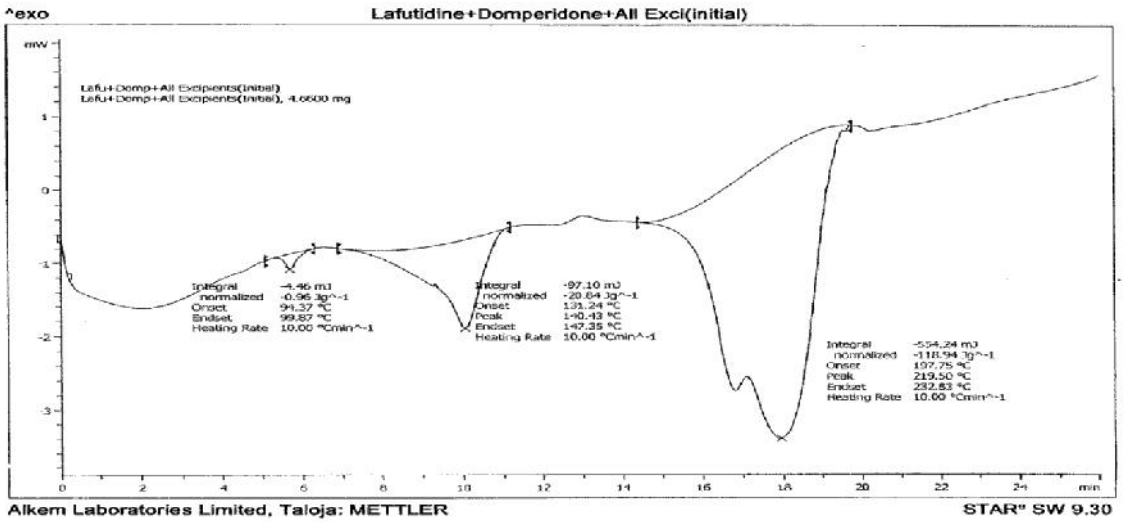


Figure 14: DSC thermogram of Lafutidine plus Domperidone Capsule

(40ºC/75% RH)

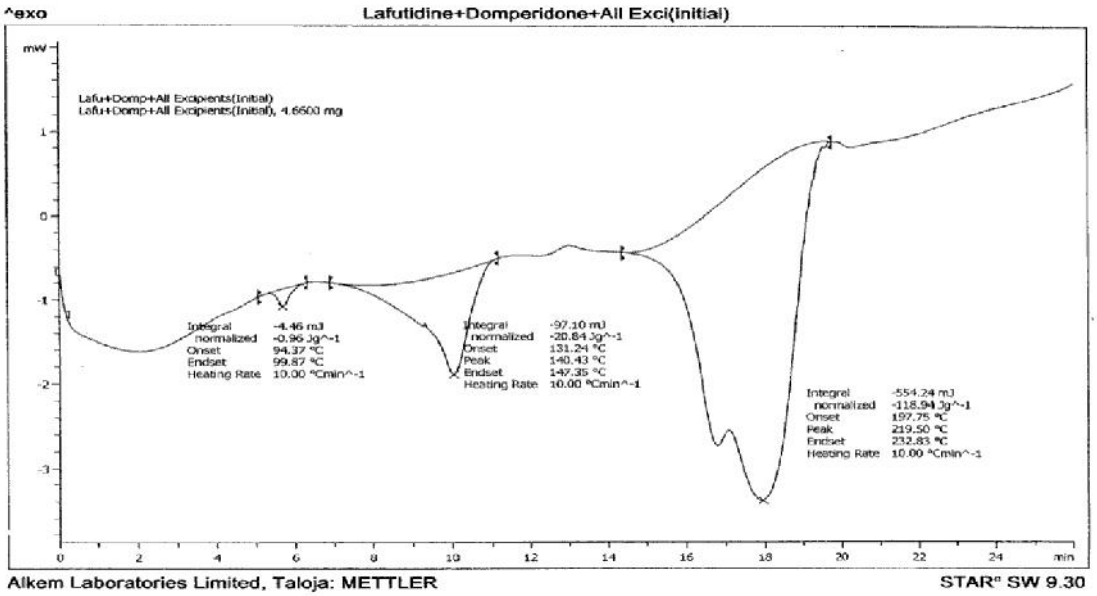
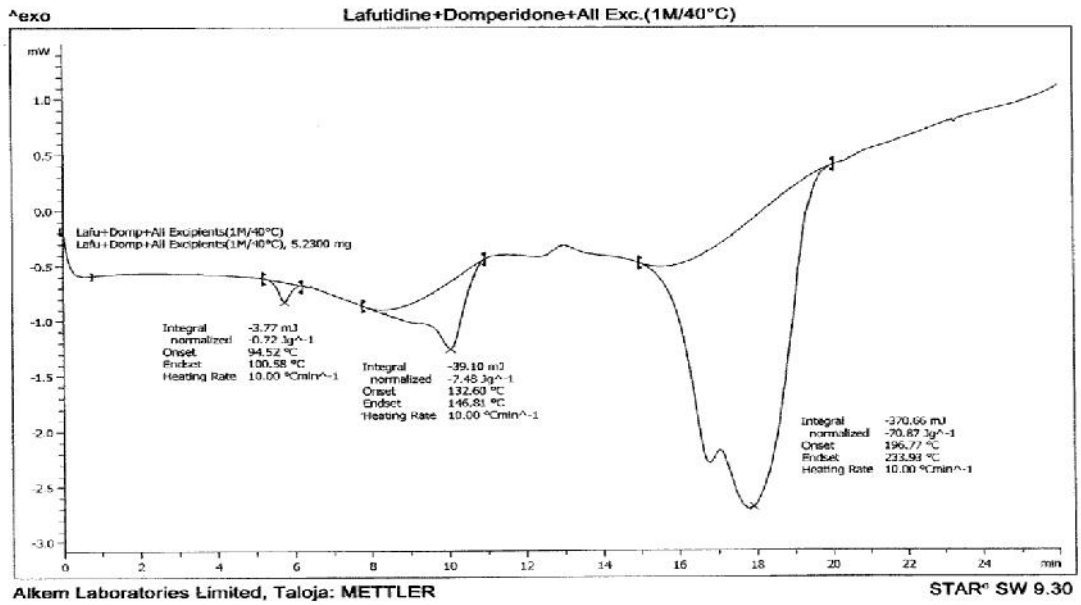


Figure 15: DSC thermogram of Lafutidine plus Domperidone Capsule 1 month

(40ºC/75%RH)



DSC Discussion:

The results indicate that, there was no significant change in Physical appearance, Assay, Related substance of drug and excipients mixture after 1 month treatment of 40°C/ 75 % RH.

DSC thermogram of Lafutidine and Domperidone shows sharp endothermic peak at 96.24°C and 215.21°C indicating the melting point of stable drug. However, the DSC Thermograms of Lafutidine and Domperidone with all excipients shows sharp endothermic peak at 94.37° C and 219.50°C.

These thermograms indicate that was no significant changes in melting point, peak shape, and area, peak location were found.

Therefore, this study revealed that there was no interaction between the drug, polymers and other excipients.

3. **In-vitro Drug Release Studies**

The Domperidone IR tablets, Domperidone SR tablets and Lafutidine blend were subjected to In-vitro dissolution studies.

The dissolution of Lafutidine blend and Domperidone IR tablet was carried out in 0.1 N HCL for a period of not more than 45 minutes. The amount of both the drugs dissolved in the prescribed media for prescribed time period was >90% which falls under the In vitro dissolution criteria given for immediate release preparations.

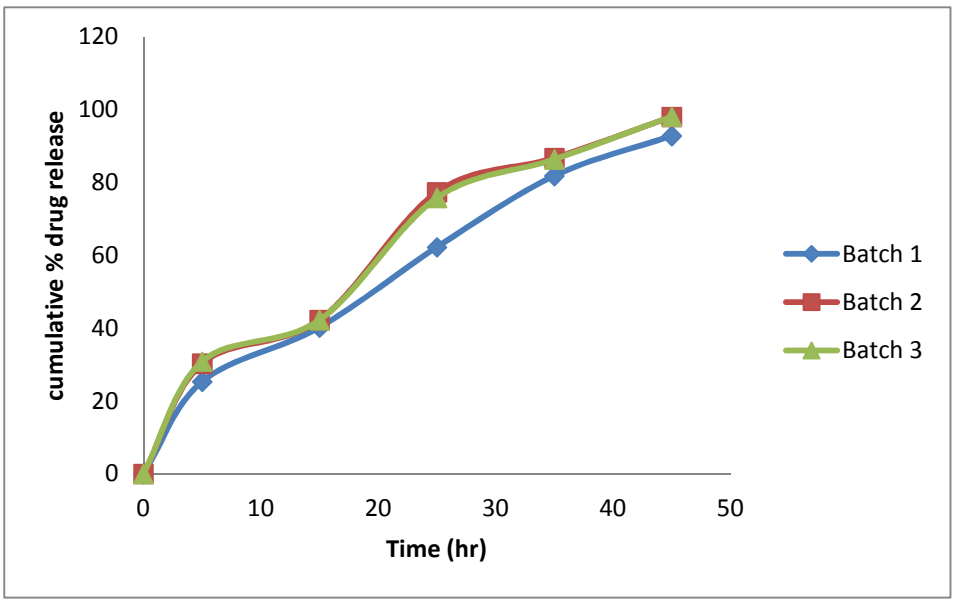
The In-vitro dissolution of Domperidone SR tablets was carried out in 0.1N HCL initially for a period of 2hrs followed by 6.8 phosphate buffer for 24hrs to achieve better In vitro In vivo correlation (IVIVC). The amount of drug dissolved at time point was observed to be within the In-House specification.

Finished Product Analytical result of Lafutidine Blend

Table 35: Dissolution in 0.1 N HCL (% Cumulative release)

Sr.No.	Time in minutes	Batch 001	Batch 002	Batch 003
1	5	25.33	30.29	30.84
2	15	40.23	42.24	42.24
3	25	62.22	75.33	77.78
4	35	81.79	86.72	86.32
5	45	92.78	98	98.07

Figure16: In vitro Drug release Profile of Lafutidine blend

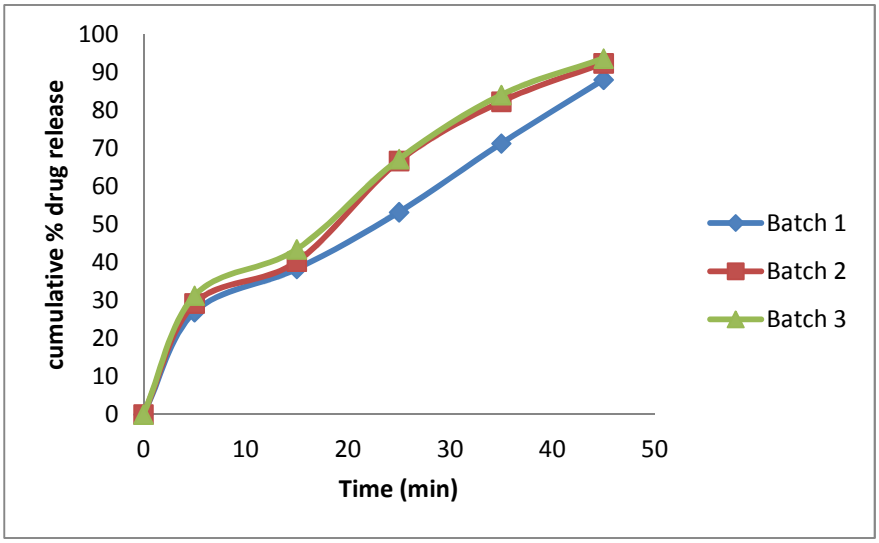


Finished Product Analytical Results for Domperidone IR Tablets

Table 36: Dissolution in 0.1 N HCL (% Cumulative release).

Sr.No	Time in minuet	Batch 1	Batch 2	Batch
1	5	26.79	29.22	31.29
2	15	38.29	40.21	43.47
3	25	53.22	66.71	67.21
4	35	71.30	82.32	84.07
5	45	88.08	92.40	93.66

Figure 17: In vitro Drug release Profile of Domperidone IR tablets



Finished Product analytical results of Domperidone SR tablets:

Table 37: Dissolution in 6.8 Phosphate Buffer: (% cumulative release)

Sr No	Time in Hour	Batch No 001	Batch no 002	Batch no 003	Batch no 004
1	2	10.8	12.4	31.7	32.1
2	4	21.90	23.4	48.2	54.3
3	8	29.98	32.6	58.3	67.1
4	12	34.5	43	68.3	74.9
5	18	40.89	48.4	74.80	83.1
6	24	59.08	52	82.7	90

Figure 18: In vitro Drug release Profile of Domperidone SR tablets (Batch 001)

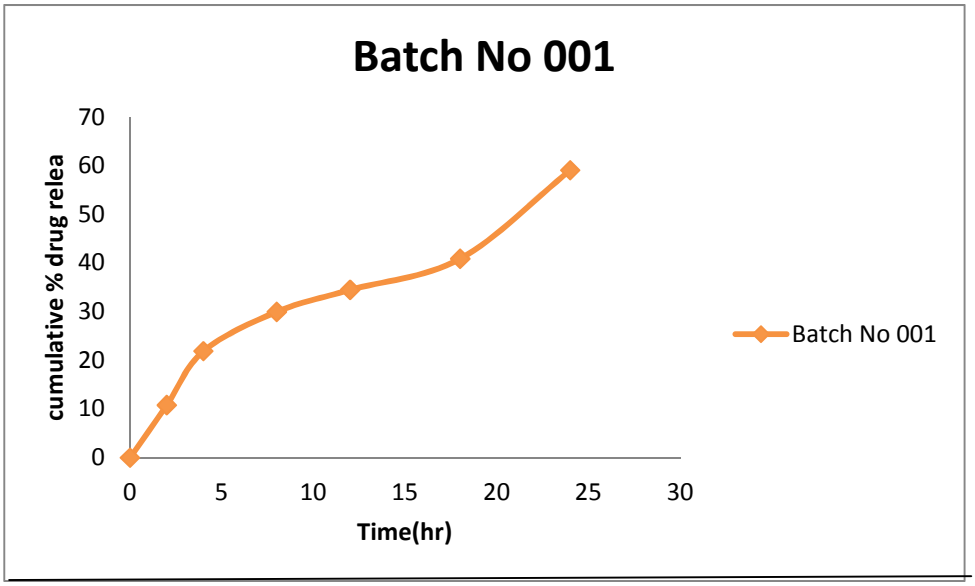


Figure.19: In vitro Drug release Profile of Domperidone SR tablets (Batch 002)

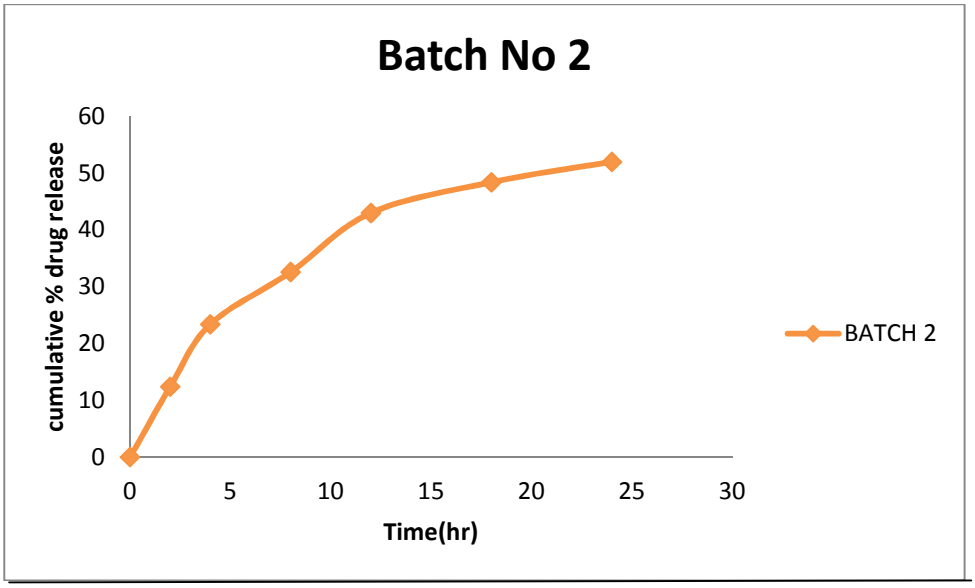


Figure.20: In vitro Drug release Profile of Domperidone SR tablets (Batch 003)

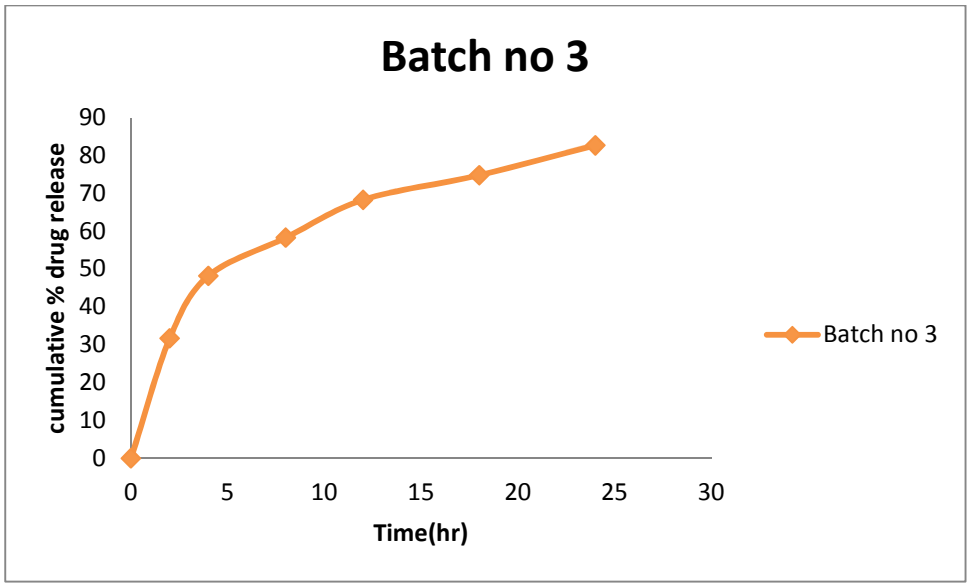
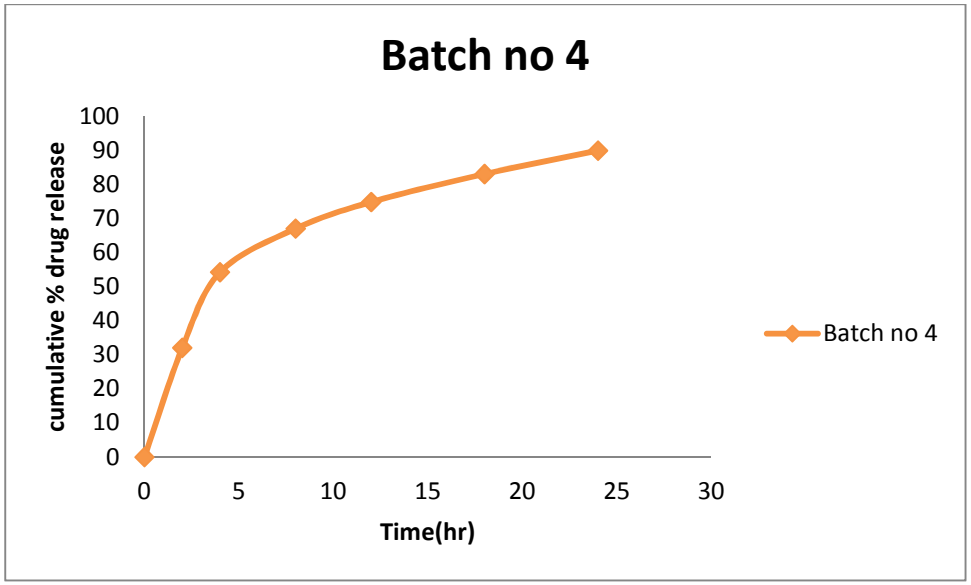


Figure 21: In vitro Drug release Profile of Domperidone SR tablets (Batch 004)



4. STABILITY STUDY

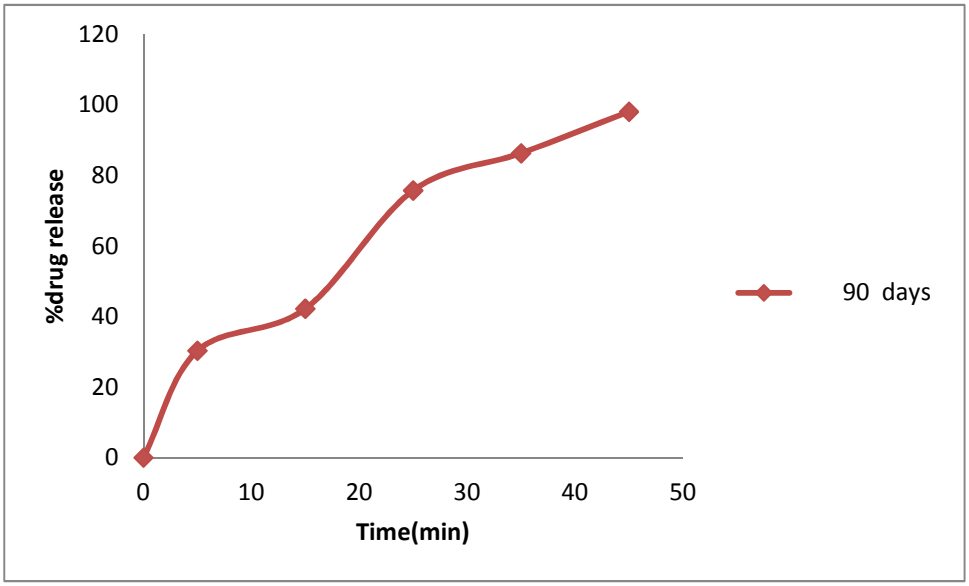
The stability a study of final trial was done for 1 month by packing in alu-alu blister in humidity chamber (40°C/75% RH) The result 1 month, 2 months and 3 month show. All parameters of formulation including physical parameters, content uniformity or dissolution profile were within specification limit. So it indicates optimized formulation were stable.

Lafutidine blend evaluated for stability studies at 40^0C / 75 % RH condition.

Figure 38: Dissolution data of percentage cumulative drug release`

Time in min	Initial Batch.No.3	30 days	60 days	90 days
5	30.84	30.83	30.82	30.31
15	42.24	42.23	42.22	42.22
25	77.78	77.76	77.75	77.75
35	86.32	86.32	86.32	86.31
45	98.07	98.07	98.06	98.06

Figure 22: vitro Drug release Profile of Lafutidine

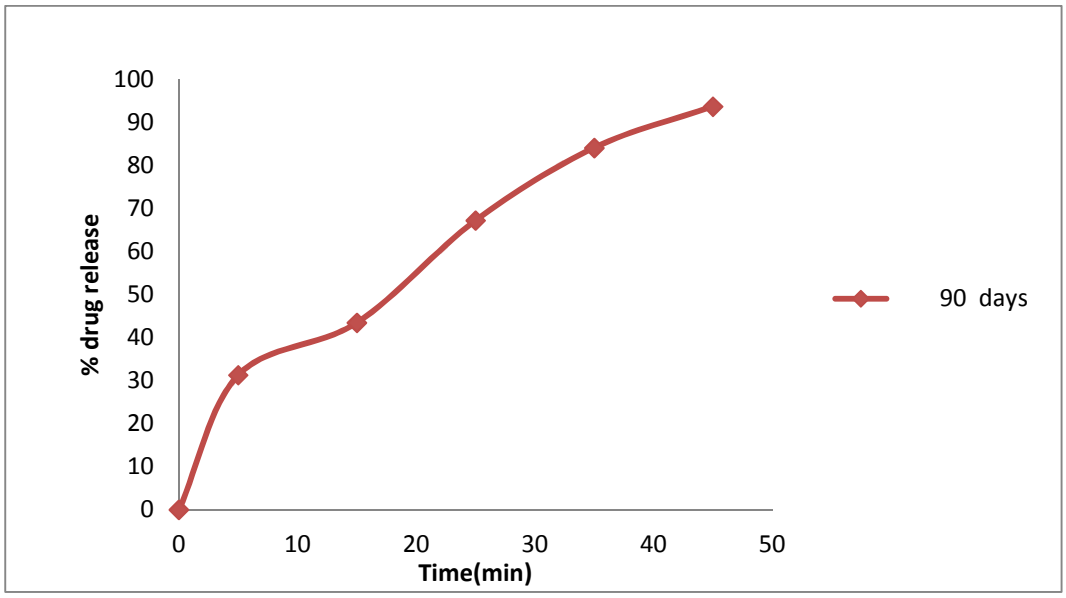


Domperidone IR Tablets

Figure 39: Dissolution in 0.1 N HCL (% Cumulative release).

Time	Initial Batch.No.3	30 days	60 days	90 days
5	31.29	31.29	31.28	31.27
15	43.47	43.47	43.45	43.44
25	67.21	67.20	67.18	67.18
35	84.07	84.06	84.04	84.04
45	93.66	93.65	93.65	93.64

Figure 23: in vitro Drug release Profile of Domperidone IR Tablets

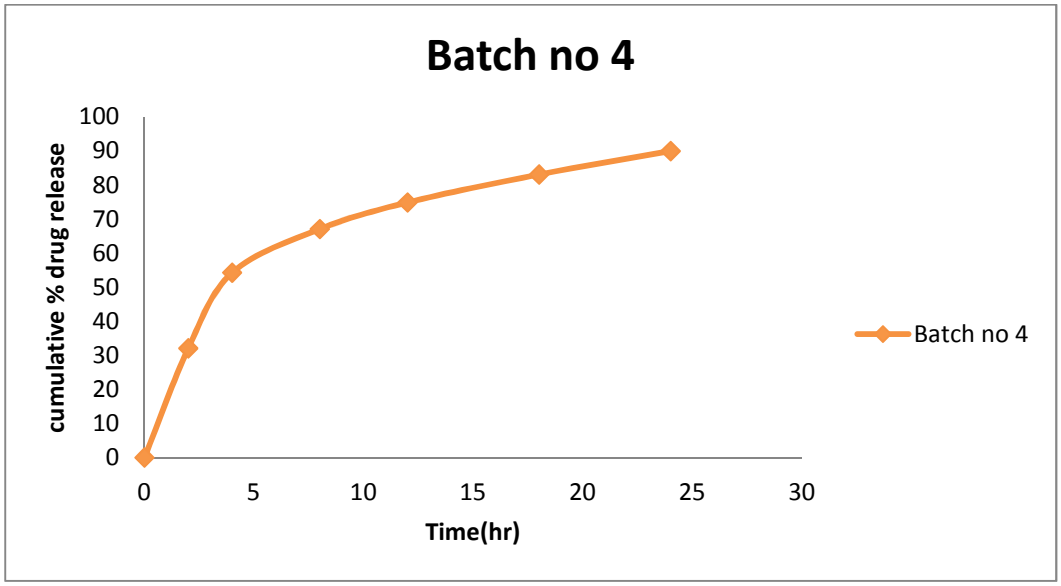


Domperidone SR tablets

Table 40: Dissolution in 6.8 PH Buffer (% cumulative release)

Time in Hour	Initial Batch.no.4	30 days	60 days	90 days
2	32.19	32.18	32.14	32.11
4	54.34	54.33	54.32	54.32
8	67.12	67.12	76.11	67.10
12	74.97	74.96	74.95	74.95
18	83.16	83.15	83.14	83.12
24	90.62	90.61	90.60	90.60

Figure 24: in vitro Drug release Profile of Domperidone IR Tablets



SUMMARY

The present research work aims at developing a novel drug delivery system consisting of a H_2 receptor blocker and a prokinetic agent.

The H_2 blocker is a newly developed potent antisecretory agent Lafutidine whereas the prokinetic agent is Domperidone.

Usually the H_2 blockers are administered once a day while prokinetic agents are prescribed thrice daily. The present formulation has been utilised to tackle the differences in dosing frequency of these two drugs. The formulation not only ensures patient convenience but also gives high relief rate.

The drug delivery system is a Capsule consisting of Lafutidine blend, Domperidone Immediate release tablets and Domperidone sustain release tablets. The Capsule dosage form is the dosage form of choice as it helps in co administration of these two drugs in two different forms to achieve better therapeutic regimen.

The immediate release forms of Lafutidine and Domperidone are administered to achieve quick relief of the disease state i.e. GERD and Dyspepsia. and the sustained release form helps in administering the drug for a period of about 24 hours to achieve prolonged therapeutic benefit.

The formulation is tested for its stability at accelerated stability conditions and from the results obtained from stability studies, it can be concluded that the formulation is therapeutically as well as physically stable over a period of 3 months.

The capsule containing Lafutidine blend and Domperidone immediate release and sustain release tablets were successfully formulated by using wet granulation method and by using different polymers.

Formulated tablets gave satisfactory results for various evaluation parameters like tablet thickness, hardness, weight variation, content uniformity and in vitro drug release.

DSC study revealed that there was no interaction between the drug, polymers and other excipients.

The formulation is tested for its stability at accelerated stability conditions and from the results obtained from stability studies, it can be concluded that the formulation is therapeutically as well as physically stable over a period of 3 months.

The present formulation has been utilised to tackle the differences in dosing frequency of these two drugs. The formulation not only ensures patient convenience but also gives high relief rate.

CONCLUSION

- From results it can be concluded, a multifunctional system was developed consisting of Lafutidine 10mg and Domperidone 30 mg (10mg +20mg) encapsulated in an capsule which can be used for the treatment of symptoms associated with GERD as well as the disease itself.
- A combination therapy of a prokinetic agent and a gastric acid lowering compound is rational and is more effective than mono therapy.

The system so developed will be a new advantage over the currently available monotherapy regimens for the treatment of Gastroesophagal reflux disease and dyspepsia.

BIBLIOGRAPHY

1) DeVault KR, Castell DO (1999). "Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. The Practice Parameters Committee of the American College of Gastroenterology". Am J Gastroenterol 94 (6): 1434–42.

2) A.D.A.M. Medical Encyclopedia, Pubmed Health (Gastroesophagal disease), Issue- 2011(http://www.ncbi.nlm.nih.gov/pubmedhealth/ PMH0001311/).

3) Marco G Patti, Gastroesophagal reflux disease, Medspace reference (http://emedicine.medscape.com/article/176595-overview#a0104)

4) http://www.aboutgerd.org/site/about-gerd/treatment/

5) Richter JE, Katz PO, Waring JP. Gastroesophageal Reflux Disease. IFFGD Brochure No. 501.

6) Thompson WG. Heartburn: nothing to do with the heart. IFFGD Fact Sheet No. 504.

7) El-Serag HB, Graham DY. Contemporary diagnosis and management of upper gastrointestinal diseases. Handbooks in Healthcare, Newtown, 2004.

8) American College of Gastroenterology Digestive Disease Specialists Committed to Quality in Patient Care.

9) http://www.mims.com/Indonesia/drug/info/lafutidine/lafutidine?type=full&mtype=generic

10) Inamori, M. et al. (2005) Early effects of lafutidine or rabeprazole on intragastric acidity: which drug is more suitable for on-demand use? J.Gastroenterol. 40, 453–458

11) Tytgat, G.N (2001) shortcomings of first generation proton pump inhibitors Eur. J.Gastroenterol. Hepatol 13 (Suppl 1) , S29-S33.

12) http://www.nature.com/gimo/contents/pt1/full/gimo54.html

13) McCallum RW, Fink SM, Winnan GR, Avella J, Callachan C. Metoclopramide in gastroesophageal reflux disease: rationale for its use and results of a double-blind trial. Am J Gastroenterol 1984; 79(3):165–172.

14) Handbook of Pharmaceutical Excipients, Fifth edition, 2006, Edited by Raymonds C Rowe, Paul J Sheskey and Sian C Owen.

15) Vyas SP, Khar RK, Controlled Drug Delivery:Concepts and Advances, 1st edition Vallabh Prakashan,New Delhi,2002.

16) Chein YW, Novel Drug Delivery System, 2nd edition, Marcel Dekker Inc; New York, 1992, Page 2.

17) Verma RK, Garg S, Current status of drug delivery technologies and future directions, Pharma Techno., 2001; 25(2), Page 1-13.

18) Brahma N. Singh Forest Laboratories, Inc., Commack, New York, U.S.A.; Kwon H. Kim Department of Pharmacy and Administrative Sciences, College of Pharmacy and Allied Health Professions, St. John's University, Jamaica, New York, U.S.A.; Drug delivery-Oral route(1242-1247), Encyclopedia of Pharmaceutical technology.

19) Robinson JR, Jantzen GM, Lee VH, Design and Fabrication of oral Controlled Release Drug Delivery Systems, In:Banker GS,Rhodes CT, editors. Modern Pharmaceutics, 3rd edition, Marcel Dekker Inc, New York 1996.

20) Syed azeem , Shaweta Sharma, International Journal of Biopharmaceutical and toxicological research, Vol-1, Issue-1, 2011.

21) Raymond baker, Eliot ohlstein, Drug discovery today: Therapeutic strategies (Elsevier), volume 4, November 4, 2007.

22) hiroshi sato, kousaku kawashima, mika yuki, hideaki kazumori, mohammad azharul karim rumi, cesar francisco ortega-cava, shunji ishihara, and yoshikazu kinoshita, Lafutidine, a novel histamine H2-receptor antagonist, increases serum calcitonin gene–related peptide in rats after water immersion–restraint stress, Izumo, Japan.

23) United States pharmacopeia.23 (1995)774,223 1.

24) Lachman L, Lieberman HA, Kanig JI, The Theory and Practice of Industrial Pharmacy, 3rd edition, Varghese Publishing House, Bombay,1987.

25) Jacobs, A.L. Determining optimum drug/excipient compatibility through preformulation testing. Pharm. Manuf. 1985, 2 (6), 43.

26) Monkhouse, D.C.; Maderich, A. Whither compatibility testing. Drug Devel. Ind. Pharm. 1989, 15, 2115.

27) Stogar – (http://www.ucb.com/_up/ucb_com_products/documents/STOGAR-April2005(050414)_tcm62-3741_tcm81-8593.pdf)

28) www.medicines.org.uk

29) www.Rx list.com.

30) www.Drugsbank.com

31) Merck index, 13 th edition, 3452.

32) European pharmacopoeia, 1475-1476.

33) British pharmacopoeia, 2000, 585-587.

34) www.medicines.org.uk

35) www.mims.com

36) http://www.mims.com/Indonesia/drug/info/lafutidine/lafutidine?type=full&mtype=generic.

37) http://www.nature.com/gimo/cntents/pt1/full/gimo54.html

38) www.Drugsbank.com

39) Merck index, 13 th edition, 7695.

40) www.Rx list.com.

41) Vyas SP, Khar RK, Controlled Drug Delivery:Concepts and Advances, 1st edition Vallabh Prakashan,New Delhi,2002.

42) L.S.C. Wan , P.W.S. Heng, L.F. Wong The effect of hydroxypropylmethyl cellulose on water penetration into a matrix system International journal pf pharmaceutics volume 73, issue 2, 1991,page 111-116.

43) Hogan, J.E. Hydroxypropyl methylcellulose sustained release technology. Drug delivery and Ind. Pharm. 15 (1989) 975-1000.

44) Tahara, K., Yamamoto, K. and Nishihata, T., Overat1 mechanism behind matrix sustained release (SR) tablets prepared with hydroxypropy1 methylcellulose 29 10. J Contr. Rel. 35 (1995) 59-66.

45) Hogan, J.E. Hydroxypropyl methylcellulose sustained release technology. Drug delivery and Ind. Pharm. 15 (1989) 975-1000.

46) Pharm, A.T. and Lee, P.I. Probing the mechanism of dmg release from hydroxypropyl methylcellulose matrices. Pharm. Res. 1 1 (1994) 1379-1384.

47) Hogan, LE. Hydroxypropyl methylcellulose sustained release technology. Drug Dev. and Ind. Pham. 15 (1989) 975- 1000.

48) Tahara, K., Yamamoto, K. and Nishihata, T. Overall mechanism behind matrix sustained release (SR) tablets prepared with hydroxypropyl methylcellulose 2910. J.Contr. Rel. 35 (1995) 59-66.

49) Shah. C.N., Zhang, G., Apelian, V., Zeng, F., Infeld, M.H. and Malick, A.W. Miction of prediction release from hydroxypropyl methylcellulose (HPMC) matrices: Effect of polyrner concentration. Pham. Res. 10 (1993) 1693- 1695.

50) Rajesh Jain, shukhjeet singh, (New Delhi India), Pharmaceutical compositions comprising of proton pump inhibitor and prokinetic agent, united states patent no 0160664 A1 2007.

51) Rao, K.V.R., Devi K.P. and Buri, P. Influence of molecular size and water solubility of the solute on its release f'rom swelling and erosion controlled polyrneric matrices. J. Contr. Rel. 12 (1990) 133-141.

52) Neville w. broad, Alan f. carmody, sustained release formulation for poorly soluble basic drugs, united states patent no 5,705,190, 1988.

53) Khan.t.f. Hydroxypropyl methylcellulose sustained release technology. Drug delivery and Ind. Pharm. 15 (1989) 975-1000.

54) M.S Nagarsenker , S.D Garad, G Ramprakash Design, optimization and evaluation of domperidone coevaporates journal of controlled release vol 63,issue 1-2,2000,page 31-39.

55) Brazel. C. S., and Peppas, N. A. Modeling of drug release from swellable polymer. Eur. J. Pharm and Biopham. 49 (2000) 4758. 25.

56) Caramella, C., Colombo, P., Conte, U., Gazzaniga A., and La Manna, A. The role of swelling in the disintegration piocess. ht. J. Pham. Tech. & M. Mfr. 5 (1984) 1-5.

57) Hogan, J.E. Hydroxypropyl methylcellulose sustained release technology. Drug delivery and Ind. Pharm. 15 (1989) 975-1000.

58) Tahara, K., Yamamoto, K. and Nishihata, T., Overat1 mechanism behind matrix sustained release (SR) tablets prepared with hydroxypropy1 methylcellulose 29 10. J Contr. Rel. 35 (1995) 59-66.

59) Muhammad Asif Khan1,2, Muhammad Saeed2, Amir Badshah Design, formulation, optimization and evaluation of sustained release tablets of Domperidone, African Journal of Pharmacy and Pharmacology Vol. 5(16), pp. 1882-1887, 2011.

60) Ip S, Chung M, Moorthy D, Yu WW, Lee J, Chan JA, Bonis PA, Lau J.Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease:Update Update of Comparative Effectiveness Review No. 1. Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease Digestion 2001;64:155–160

61) Rockville, Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease: Update. Comparative Effectiveness Review No. 29. (Prepared by Tufts Medical Center Evidence-based Practice Center under Contract No. HHSA 290-2007-10055-I.) AHRQ Publication No. 11-EHC049-EF., MD: Agency for Healthcare Research and Quality. September 2011.

62) H. Yamagishi, T. Koike, S. Ohara et al., "Stronger inhibition of gastric acid secretion by lafutidine, a novel H receptor antagonist, than by the proton pump inhibitor lansoprazole," World Journal of Gastroenterology, vol. 14, no. 15, pp. 2406–2410, 2008.

63) Onodera S, Shibata M, Tanaka M, et al. Gastroprotective mechanism of lafutidine, a novel anti-ulcer drug with histamine H2-receptor antagonistic activity. Arzneimittelforschung 1999; 49:519–26.

64) Bhupesh Dewan1 and Nisha Philipose Lafutidine 10 mg versus Rabeprazole 20mg in the Treatment of Patients with Heartburn-Dominant Uninvestigated Dyspepsia:A Randomized,Multicentric Trial Gastroenterology Research and Practice Volume 2011, Article ID 640685, 8 pages

65) Bauerfeind P, Hof R, Hof A, Cucala M, Siegrist S, von Ritter C, Fischer JA, Blum AL Effects of hCGRP I and II on gastric blood flow and acid secretion in anesthetized rabbits. World Journal of Gastroenterology, vol. 14, no. 15, pp. 2445–2470, 2009..

66) Takanobu Uesugi, MD, Katsuya Mikawa, MD, Kahoru Nishina, MD, Osamu Morikawa, MD, The Efficacy of Lafutidine in Improving Preoperative Gastric Fluid Property: A Comparison with Ranitidine and Rabeprazole Department

of Anesthesia and Perioperative Medicine, Faculty of Medical Sciences, Kobe University Graduate School of 1Medicine, Kobe, Japan 2002.

67) Kazuro Ikawa, Tomohiko Shimatani, Seiichi Hayato Pharmacokinetic and pharmacodynamic properties of lafutidine after postprandial oral administration in healthy subjects: comparison with famotidine. Biol Pharm Bull. 2007 30 (5):1003-6.